- The statements about the evidence against confounding by smoking given by restriction of the cohort should be qualified by the assumptions required to justify them, or deleted.
- The SAB had no recommendations for further analyses.
- The reference to three methods is confusing. There are actually only two, the restricted cohort and the Richardson analysis for which two exposure metrics are explored.

3.2.6.3. Quantification of Inhalation Unit Risk

Question 3. In order to derive an IUR which represents the combined risk of mortality from lung cancer or mesothelioma, a cancer-specific unit risk for each tumor type was calculated according to the Guidelines for Carcinogen Risk Assessment (U.S., EPA, 2005; Sections 3.2 and 3.3) by linear extrapolation from the corresponding POD (i.e., the lower 95% confidence limit on the exposure associated with 1% extra risk of lung cancer or 1% absolute risk of mesothelioma mortality). The IUR was then determined as a combined upper bound risk estimate for mortality considering both cancers. Has this approach been appropriately conducted and clearly described?

The SAB found the description of the procedure used to be clear but considered the justification for the independence assumption to be lacking in depth. The EPA should provide a discussion of the potential consequences of assuming that the estimated IURs for mesothelioma and lung cancer mortality are independent, noting the possibility that the upper bound on the IUR may be understated if the risks are positively correlated. The document may refer to the 1994 NRC report, which suggested that treating different tumor occurrences as independent is "not likely to introduce substantial error in assessing carcinogenic potency". However, the document should acknowledge that this statement was made in the context of animal bioassays and that human populations are more heterogeneous in risk factors related to mesothelioma and lung cancer mortality. If any risk factors are shared across outcomes and not accounted for in the modeling, the risk estimates generated by the different models are likely correlated. Given the small size of the data set, and lack of an appropriate statistical method, this correlation cannot be estimated reliably. One approach might be to undertake bounding analysis on the lifetime risk estimates using, for example, the Fréchet inequality for disjunctions (Fréchet, 1935) that makes no assumption about the nature of the dependence. This analysis could reveal how large the impact of dependence might be. At the very least, the restrictive assumption of independence must be mentioned and the potential consequences of a violation of this assumption must be discussed.

Recommendations:

- The EPA should acknowledge that the assumption of independence is a theoretical limitation of the analysis, and should provide a fuller justification for this assumption. EPA has cited the NRC (1994) analysis as suggesting the impact of this issue is likely to be relatively small. This view is also echoed in the EPA's (2005) *Guidelines for Carcinogen Risk Assessment.* These provide the basis for a default assumption. However, it would be preferable if this assessment discussed the evidence base and rationale for lung cancer and mesothelioma specifically.
- As a sensitivity analysis, the EPA should consider quantitatively accounting for dependence in the risks of mesothelioma and lung cancer mortality either using a method that models the dependence explicitly, or a bounding study that evaluates the numerical consequences of the assumption of independence.

3.2.6.4. Adjustment for Mesothelioma Mortality Under-ascertainment

Question 4. Please comment on the adjustment for mesothelioma mortality under-ascertainment. Is this adjustment scientifically supported and clearly described? If another adjustment approach is recommended as the basis for the IUR, please identify that approach and provide the scientific rationale.

The number of mesothelioma deaths was adjusted for under-ascertainment stemming from inadequate coding used in death certificates. The procedure used is not described in any detail, but can be found in the Kopylev et al. (2011) reference. A total of 18 mesotheliomas were observed in the Libby cohort from 1980 to 2006. The estimated number of 24 mesotheliomas was obtained after using a Monte Carlo analysis. The ratio of 24 to 18 yields the median of 1.33. The Kopylev manuscript also provides a figure of 1.39 in Table 3, which is the mean later reported in the EPA report. The EPA method appears to be scientifically supported, but is not clearly described. This section should be expanded and a much more detailed statement of how the numbers were arrived at should be provided.

No additional adjustment approach is described in the EPA report. The authors should provide an additional estimate using the 37% figure mentioned on page 46 of the Kopylev et al. (2011) reference. This is the percentage of mesothelioma cases that would be missed using previous histopathological analyses of cancer registry data. Using 37% would yield an estimate of about 29 mesothelioma cases instead of 24. The median ratio would then be 1.61 instead of 1.33. This number, and its related mean, should be utilized to provide a separate analysis of unit risk for comparison purposes.

3.2.6.5. Characterization of Uncertainties

Question 5. Please comment on whether the document adequately describes the uncertainties and limitations in the methodology used to derive the IUR and whether this information is presented in a transparent manner.

The SAB commends the EPA for summarizing (in Section 5.4.6.1 of the draft document) the many sources of uncertainty considered in the course of this document and evaluating, at least qualitatively, and sometimes quantitatively, the direction and magnitude of the likely impact of each source of uncertainty.

However, the SAB noted that most of what the document has accomplished is through targeted sensitivity analyses that examine one assumption at a time, while holding all others more or less constant. For example, the agency has indeed done a thorough job of exploring sensitivity of the IURs to a range of investigator analyses of lung cancer (Table 5-20) and mesothelioma (Table 5-21) for the Libby worker subcohort, and to a wide range of assumptions about the exposure metrics to be used in the basic models (e.g., Table 5-9). The basic underlying models chosen for lung cancer and for mesothelioma are the same.

The sensitivity analyses in the document are individually well described, appear well-done and provide reassurance, under the assumptions of the basic models and approaches chosen to estimate the IUR, that the particular exposure metric and lag, for example, do not appear to make a big difference in the value of the IUR. However, they are currently presented somewhat in isolation, and thus do not take into account the magnitude and likelihood of multiple sources of uncertainty in the same analysis or address the overall distribution of uncertainty in the IUR. Consequently, the SAB did not think that the following statement had been fully justified:

…the EPA's selected combined IUR of mesothelioma and lung-cancer mortality accounts for both the demonstrated cross-metric uncertainty as well as several additional uncertainties, which could have resulted in underestimates of the mesothelioma and lung-cancer mortality risks (p 5-105, lines 1-5).

As noted in response to question 1 in Section 3.2.6.1 above, the SAB identified that model uncertainty is an important source of uncertainty that might well not be accounted for by using the 95% UCL on the IUR and the combined IUR — or at least that had not been represented by the sensitivity analyses provided.

Recommendations:

- The SAB recommends that a more straightforward and transparent treatment of model uncertainty would be to estimate risks using a more complete set of plausible models for the exposure-response relationship (discussed in response to question 1 in Section 3.2.6.1), including the Poisson models. This sensitivity analysis would make the implications of these key model choices explicit.

- The SAB recommends that, as an initial step in conducting an integrated and comprehensive uncertainty analysis, the agency provide a tabular presentation and narrative evaluation of the IUR estimates based on a reasonable range of data selections (e.g., all or part of the earlier hires as well as the "preferred" subcohort), model forms and input assumptions (as discussed, in the response to question 1 in Section 3.2.5). These input assumptions should include *inter alia* exposure metrics and externally defined parameters, as discussed in the response to question 1 in Section 3.2.5. As noted in the current cancer risk assessment guidelines (EPA, 2005, page 3-29):

  > The full extent of model uncertainty usually cannot be quantified; a partial characterization can be obtained by comparing the results of alternative models. Model uncertainty is expressed through comparison of separate analyses from each model, coupled with a subjective probability statement, where feasible and appropriate, of the likelihood that each model might be correct (NRC, 1994).

The SAB notes that ideally, the agency would develop a quantitative characterization of the overall uncertainty in its IUR estimates by incorporating the major sources of uncertainty the agency has identified in its evaluation. However, the SAB recognizes the challenge of conducting such an analysis, and is not recommending that it be undertaken at this time.

4. LONG-TERM RESEARCH NEEDS

4.1. Epidemiology

It would be informative and very important for NIOSH and ATSDR to continue monitoring mortality among Libby workers (including those residing in Libby and nearby towns such as Troy, Montana) and residents of Libby and nearby towns, respectively, to determine the number of new lung cancers, mesotheliomas, and non-malignant pulmonary diseases (i.e., asbestosis) in these two populations.

The last occupational ascertainment was through 2006; an additional five years of data should now be available. In addition to a dose-response evaluation, an overall SMR should be calculated for lung cancer in this population by comparison to both the Montana and U.S. populations.

The previous ATSDR community SMR mortality survey was from 1979-1998. It should now be extended through 2011 and should include an analysis specific for community, non-occupationally exposed, individuals. Early-life exposure to LAA could possibly be obtained from surrogate interview information from the community population. Smoking, occupational, and residential histories should be obtained for the lung cancer, mesothelioma, and non-malignant respiratory disease (i.e., asbestosis) categories. Data concerning previous Libby residents who had moved away (and died in other states) would need to be obtained by means of a special effort of ATSDR.

A community cross-sectional respiratory health screening was conducted in Libby by ATSDR in 2000 and 2001. A non-malignant respiratory health update since then would be useful. The appropriate smoking, occupational, and residential histories should be included.

4.2. Mode of Action

It would be valuable for future research on LAA mode of action to focus on biomarkers that are more clearly and specifically related to non-cancer endpoints (i.e., asbestosis) or cancer endpoints (e.g., mesothelioma). Critical genotoxicity studies including mutagenesis and chromosomal aberration studies have not been investigated with LAA. Inhalation studies in animal models that can provide mechanistic and dose-response relationship should be conducted.

4.3. Future Development of a TEM Method for PCM Equivalency

EPA needs to develop a transmission electron microscopy (TEM) method that provides equivalent data to phase contrast microscopy (PCM). This TEM method development must first recognize fundamental differences between TEM and PCM analysis. Areas that need better definition include differences in analyzable areas, changes in PCM resolution over time, measuring complex fibrous structures, measuring obscured fibers, defining TEM analysis parameters more succinctly, recognition of several other measurement characteristics of importance (such as surface area), defining inter-laboratory variations and their causes, as well as other areas related to analysis.

Other areas of analysis may include but not limited to: differences between PCM reticule areas and TEM grid opening areas that create biases; TEM rules with regard to fibers obscured by grid bars which create positive bias in TEM results; measurement of obscured, complex arrangements of fibers by TEM that differ from PCM counts; TEM measurement errors associated with fibers of various widths; differences between laboratories with interpretation of TEM counting rules; differences in magnification and orientations used for analysis; and other issues which create variation between analyses.

APPENDIX C – 15

EXCERPTS

In the Matter of:

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY SCIENCE ADVISORY BOARD

LIBBY AMPHIBOLE ASBESTOS REVIEW PANEL MEETING
May 1, 2012

MERRILL LAD
1325 G Street NW, Suite 200, Washington, DC
Phone: 800.292.4789 Fax:202.861.3425

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

SCIENCE ADVISORY BOARD

LIBBY AMPHIBOLE ASBESTOS REVIEW PANEL MEETING

Meeting Via Teleconference

Tuesday, May 1, 2012

(Transcript Revised July 2012 Following Review by Counsel)

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DR. KANE: Do other members of the panel have any comments on this?

MALE SPEAKER: Well, I understand Lianne's point, and I don't have any problem trying to add a sentence or two in that regard. I will say that it's not put in for the current report because I think that it's probably too late to include anything new, but I work on a regular basis on a different project altogether with Jim Lockey who's the senior author of the work -- senior deputy on the Marysville cohort.

And they have a paper, I believe it's actually been accepted already, but I'm not entirely sure about that where they've done HRTC scanning of members of the Marysville cohort. And they are going to have data about some clinical interstitial fibrosis or asbestos that's related to the exposure. And that's down the line, but it's coming.

So while it may not be pertinent to this report, it's I think Lianne's point that we should establish that all radiographic abnormalities should be considered in the future is one worth adding to the section.

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DR. KANE: Other panel members agree with that?

UNIDINTIFIED SPEAKER: MMO?

FEMALE SPEAKER: And I think the particular point that the panel was making is whether, if you actually look at the papers that were included the diffuse pleural thickening, the fact the numbers that she said changed very little.

MALE SPEAKER: Right.

DR. KANE: But the general recommendation that these should be considered in future I think that was pretty clear when stated.

DR. SHEPPARD: Yeah. Yeah. It's maybe not relevant for this particular response but I think I felt like it wasn't completely clear throughout the entire document, but I haven't identified where I might recommend changes, but I think we'd want to be -- we want to be clear about looking forward versus specific changes to this document.

DR. KANE: Okay. We will definitely flag that one to look at very carefully.

Any other issues related to the

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radiographic changes and LPT and the derivation for the RfC?

DR. SALMON: This is Andy Salmon here. I think it's probably worth just putting in a very small side comment to the effect that we are looking at these radiographic changes as an adverse effect in their own right. We are not necessarily arguing whether or not they progress to some other disease entity. And that it needs to be considered as an adverse in its own right.

DR. KANE: I think that is clearly stated but I will make sure that that is clear.

DR. SALMON: I say that mainly because some comments have attempted to obfuscate that point.

DR. KANE: I don't think the members of the panel meant to do that.

DR. SALMON: No, I don't mean comments from members of the panel. Members of the panel have been absolutely clear on that, in my opinion. I mean the public comments.

DR. KANE: Absolutely. All right. We will check. I will carefully read that part of the report

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and make sure that our statement is clear.

DR. SALMON: Thank you.

DR. KANE: Thank you. All right. With respect to charge 3 refers to the database laboratory study, what kinds of mechanisms may be responsible for the noncancer endpoint this is begins on page 19 of the draft summary.

Does anyone have any substantive comments to make here? I'll particularly ask the people who considered this. Are you here now. Jeff? David Bonner?

DR. BONNER: Yes, I'm here.

DR. KANE: Do you have any comments or questions on this section?

DR. BONNER: No.

DR. HEI: I am here. I thought that the section is pretty straightforward in terms of the mechanisms that promote the inflammatory response and the many of the noncancerous lesions that was observed. So based on what is a lesion, I have no further addition.

DR. KANE: Excellent. Okay. At this point

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when we consider our full discussion on localized pleural thickening and the derivation of the RfC and the discussions that we will make sure we have made it very clear about what we consider in terms of the radiographic changes and the fact that these are an adverse effect, not adverse effect nevertheless. Any other comments or anything we should clarify at this point?

DR. SHEPPARD: This is Lianne Sheppard. I was -- I wrote some notes to myself about whether the last paragraph of this response on page 20, lines 18 through 22 needed a little bit more elaboration. And I don't have any suggestions. I just guess I wanted to revisit that.

DR. KANE: Do other members of the panel have comments?

DR. BONNER: This is Jamie Bonner. I think I lost you guys. I pressed the wrong button trying to mute back in. I had no further comments on the non-cancer study for animals.

DR. KANE: Thank you, Jamie.

DR. BONNER: You are welcome.

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DR. KANE: I'm glad you are back.

DR. BONNER: Thank you. Sorry about that.

DR. KANE: All right. Lianne Sheppard raises some questions on lines 18 through 22 on page 20. Lianne, you did specifically comment about clarifying who SAB is agreeing with. We've changed that to considers a more conservative approach and deriving the RfC is therefore appropriate policy choice. I will clarify that. But do you think we need further discussion in this paragraph?

DR. SHEPPARD: Well, I guess I'm just making sure that nobody else does. I am okay if -- because I didn't write this section, I'm okay with it. I just wanted to raise it and make sure that everybody was okay with it.

DR. KANE: Are the members of the panel, you satisfied with this that it is clear? Okay. Again, I thank you.

DR. BALMES: Yes, this is John Balmes. Do you think there might be misinterpretation possibilities with a more conservative approach? I mean do you mean health conservative or I think that's

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what we mean, right?

DR. KANE: Could the members of the panel who wrote this clarify that? What is meant by that?

DR. BALMES: I think that could be interpreted possibly different ways. That's my only -- I don't know who wrote it.

DR. KANE: Does anyone wish to comment?

DR. BALMES: If we mean public health conservative, we should say that, I think.

DR. KANE: A more conservative approach.

MALE SPEAKER: Does that mean less aggressive on the part of EPA picking an RfC because there's a limited and complex database, or does it mean because we have a limited, complex database we should be public health conservative? I think --

DR. SHEPPARD: You mean more protective of public health?

MALE SPEAKER: Yes.

DR. SHEPPARD: Yeah. I think we should add that language.

DR. KANE: I like that, a more conservative approach that is more protective of public health.

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MALE SPEAKER: Yeah.

DR. KANE: Does everyone agree with that?

DR. HEI: That's fine.

FEMALE SPEAKER: Yes.

MALE SPEAKER: Yeah, I would agree.

DR. KANE: Okay.

MALE SPEAKER: Dr. Hei, you and I are protesting.

MR. BUSSARD: This is David Bussard again. I guess I'm not sure more conservative than what? I am not sure about the more in that sentence, what you mean by it?

DR. HEI: Yes.

MALE SPEAKER: Why don't we just say a conservative approach, i.e. protective of public health; leave out the more.

DR. KANE: Yes. I think that's appropriate. Do the members of the panel agree? A conservative approach that is more protective of public health?

MALE SPEAKER: Yes.

DR. KANE: Okay.

APPENDIX C – 16

From: Kane, Agnes
To: Diana-M Wong/DC/USEPA/US@EPA
Subject: Re: Fw: Edited Response to Question 2 on Noncancer Health Effects
Date: 07/09/2012 11:17 AM

Dear Diana,
I agree with Carrie's changes.
Sincerely,
Agnes

Agnes B. Kane, MD, PhD, Chair
Department of Pathology and Laboratory Medicine
Brown University
Email: Agnes_Kane@Brown.Edu
Phone: 401-863-1110

On Mon, Jul 9, 2012 at 10:11 AM, Diana-M Wong <Wong.Diana-M@epamail.epa.gov> wrote:

> Dear Agnes,
>
> Welcome back!
>
> Attached please find Dr. Redlich's edits on response to Question 2. Thanks.
>
> Diana
>
> Diana Wong, Ph. D., DABT
> Toxicologist and Designated Federal Officer
> USEPA
> Science Advisory Board Staff Office
> MC: 1400R
> 1200 Pennsylvania Ave, N.W.
> Washington, DC 20460
>
> Phone:(202) 564-2049
>
> ----- Forwarded by Diana-M Wong/DC/USEPA/US on 07/09/2012 10:07 AM -----
>
> From: "Redlich, Carrie" <carrie.redlich@yale.edu>
> To: Diana-M Wong/DC/USEPA/US@EPA, John Balmes <jbalmes@medsfgh.ucsf.edu>, "Newman, Lee" <Lee.Newman@ucdenver.edu>
> Cc: "Salmon, Andy@OEHHA" <Andy.Salmon@oehha.ca.gov>, Agnes Kane <agnes_kane@brown.edu>, "Morton.Lippmann@nyumc.org" <Morton.Lippmann@nyumc.org>, Susan Woskie <Susan_Woskie@uml.edu>, "David Kriebel" <David_Kriebel@uml.edu>
> Date: 07/08/2012 05:30 PM
> Subject: Re: Edited Response to Question 2 on Noncancer Health Effects
>
> ---
>
> Diana
> I agree that it IS OK to leave in that plaques are indicators of increased risk for the future development of lung cancer, in agreement with ATS Asb reference.
> I have made some additional minor edits (see attached) mainly deleting a few phrases per the "less is more" principle, wanting to avoid statements that critics may attack.
> Carrie
> John and Lee – Are you OK with?
>
> On 7/5/12 7:02 PM, "Diana Wong" <Wong.Diana-M@epamail.epa.gov> wrote:
>
> Dear All,

I checked the ATS, (2004) reference, which is available in the reference section of the HEROized Libby assessment.

On page 705, it did state: "The presence of plaques is associated with a greater risk of mesothelioma and of lung cancer compared with subjects with comparable histories of asbestos exposure who do not have plaques".

On page 707, it stated: "Plaques are indicators of increased risk for the future development of asbestosis".

However, we are still waiting for the input of our pulmonologists experts to let me know if "lung cancer" should be deleted. Thank you very much.

Diana

Diana Wong, Ph. D., DABT
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Washington, DC 20460

Phone:(202) 564-2049

----- Forwarded by Diana-M Wong/DC/USEPA/US on 07/05/2012 06:45 PM -----

From: Diana-M Wong/DC/USEPA/US
To: jbalmes@medsfgh.ucsf.edu, Lee.Newman@ucdenver.edu, carrie.redlich@yale.edu, Susan_Woskie@uml.edu, David_Kriebel@uml.edu
Cc: "Salmon, Andy@OEHHA" <Andy.Salmon@oehha.ca.gov>, agnes_kane@brown.edu, Morton.Lippmann@nyumc.org
Date: 07/03/2012 11:49 AM
Subject: Fw: Edited Response to Question 2 on Noncancer Health Effects

---

Dear All,

Dr. Lippmann commented on p. ii, line 6,7 of the cover letter that "lung cancer" should be deleted. To be consistent, lung cancer is also deleted in the response to question 2. Please review and let me know if you have other suggestions. Thanks.

(See attached file: dw Response to Question 2 on Noncancer Health Effects.docx)

Diana Wong, Ph. D., DABT
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----- Forwarded by Diana-M Wong/DC/USEPA/US on 07/03/2012 11:41 AM -----

From: Diana-M Wong/DC/USEPA/US
To: jbalmes@medsfgh.ucsf.edu, Lee.Newman@ucdenver.edu, carrie.redlich@yale.edu, Susan_Woskie@uml.edu, David_Kriebel@uml.edu
Cc: "Salmon, Andy@OEHHA" <Andy.Salmon@oehha.ca.gov>, agnes_kane@brown.edu
Date: 07/02/2012 05:50 PM
Subject: Fw: RE: Public Comments Posted on Our Website

Dear All,

Attached please find Karl Bourdeau's comments on June 25, Dr. Salmon's response to these comments on LPT, and the subgroup response to question 2 on the selection of critical effect for the derivation of RfC.

(See attached file: Bourdeau June 25 no sig.pdf) (See attached file: Response to Question 2 on Noncancer Health Effects.docx)

Please let me know ASAP if any changes to the response to question 2 is needed, based on the comments, and Dr. Salmon's response to comments.

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----- Forwarded by Diana-M Wong/DC/USEPA/US on 07/02/2012 05:30 PM -----

From: "Salmon, Andy@OEHHA" <Andy.Salmon@oehha.ca.gov>
To: Diana-M Wong/DC/USEPA/US@EPA
Date: 06/27/2012 05:13 PM
Subject: RE: Public Comments Posted on Our Website

Having taken a look at these comments, I do need to respond to their mischaracterization of my earlier remarks about LPT as a toxicity endpoint. They appear to think that I was discounting the possibility that LPT was associated with changes in lung function. I never said anything of the sort. In the first place, the discussion about where LPT stands on the overall mechanistic pathway started in the context of mesothelioma rather than lung function changes. The general conclusion of the panel (with which I agree) is that there certainly are common elements to the causative pathways for mesothelioma and LPT, but it is not correct to see LPT as an obligatory precursor to mesothelioma, i.e. not all LPT lesions will progress to mesotheliomas and not all mesotheliomas arise by progression of LPT lesions. But both types of lesion arise as the result of the cellular damage induced by the persistent fibers and other associated effects. With regard to lung function changes, the point of my remarks is that regardless of whether or not LPT is associated with observable lung function changes, it is in and of itself an irreversible pathological change in tissue structure. Risk assessment guidelines identify that endpoint as a suitable (and indeed, fairly severe) endpoint for use in risk assessment, regardless of whether functional changes are observed as a result of or associated with that finding. The panel subsequently discussed the question of whether, in addition to LPT, the amphibole exposures were also associated with observable lung function changes in the dose range of interest, and it was concluded that they were. It appears that LPT findings are not invariably associated with observable lung function changes, or vice versa: how much of this is due to relative insensitivity and imprecision of these clinical evaluations, or merely to the fact that they are seldom done simultaneously on the same subject, is unclear. However, the risk assessment conclusions are simpler: both LPT and lung function changes are separately demonstrable effects of exposure to amphiboles, which may be considered independently in determining dose response relationships for adverse effects.

From: Diana-M Wong [mailto:Wong.Diana-M@epamail.epa.gov]
Sent: Monday, June 25, 2012 11:32 AM
To: Diana-M Wong
Subject: Public Comments Posted on Our Website

Dear Panel Members,

A set of public comments submitted by Karl Bourdeau of Beveridge & Diamonds is posted on our website for your consideration. The link is provided below:

http://yosemite.epa.gov/sab/sabproduct.nsf/MeetingCal/DE16F40DF2BE9271852579FB0054C2BF?OpenDocument
<http://yosemite.epa.gov/sab/sabproduct.nsf/MeetingCal/DE16F40DF2BE9271852579FB0054C2BF?OpenDocument>

The pdf file is also attached.

(See attached file: Bourdeau June 25 no sig.pdf)

Sincerely,

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Carrie A. Redlich, MD, MPH
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Cell Phone [redacted]
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(See attached file: cr edits.Response to Question 2 on Noncancer Health Effects.docx)

APPENDIX C – 17

From:	Redlich, Carrie
To:	Diana-M Wong/DC/USEPA/US@EPA; Agnes Kane
Subject:	Word of explanation re LPT associated with increased risk meso, lung ca
Date:	07/28/2012 09:04 PM
Attachments:	asb pleural meso[3].pdf asb plaques lung cancer.pdf Reid Addit risk meso wittenoom OEM 2005.pdf

Agnes/ Diana
I found this in my outbox – not sure if sent earlier in the week- may be duplicate email
carrie

Agnes / Diana
I thought I should add a word of explanation for deleting a sentence that generated so much attention (below - I didn't write it) and my other more minor edits.
While the ATS asbestos document does say LPT associated with increased risk asbestosis, ca, meso, it cites only 2 references to support LPT associated with increased risk of mesoth and lung cancer (beyond exposure history). Most clear, and what we discussed at our meeting and prior calls, was that LPT associated with reduced lung function, which a number of well done studies document. We suggested EPA further highlight this literature and added a few additional references. Not a big deal / change.
I had been uncomfortable with LPT being predictive / associated with increased risk of meso, lung cancer, so I had done some searches of the epi literature (see attached). The question is complicated by 1) confusion if referring to plaques as a marker of asbestos exposure vs increased risk beyond estimated exposure (the real Q), and 2) studies have mostly used occupational history for exposure assessment.
One of the better articles (Reid) and brief lit search attached. (Reid already cited by EPA somewhere. Don't think EPA needs to add any refs).
Bottom line – while ATS statement likely correct, **there's not much evidence to support LPT and increased risk meso, lung ca (beyond exposure),** and as mentioned, no need to go there. It's confusing and nonmalignant changes sufficient justification as endpoint, and it's just opening up EPA for criticism. This is referring to LPT and risk of meso, lung cancer. There is good data that supports LPT and reduced lung function. (my edits tried to clarify this).
Sorry didn't bring this up on the call – I was hesitant to start a whole discussion about. I looked over articles etc more carefully when doing edits and realized that while "associated" better than "predictive", even better to omit.

As you know, asbestos differs somewhat from pollutants such as ozone, as there are well known clinical entities caused by asbestos. It may be helpful for the EPA to more fully explain Rfc version of health effect vs clinical disease. ATS document focused on clinical asbestos-related disease. Clinicians / others are so used to reassuring patients that plaques are no big deal, don't affect lung function (esp as typically past exposure can't do anything about), that they may need an extra reminder as far as Rfc / the public health perspective.

It took me a while to remember this after "minimizing" plaques with individual patients for so long.

Hope this helps.

Carrie

On 7/25/12 6:52 PM, "Carrie Redlich" <carrie.redlich@yale.edu> wrote:

"Additionally, the presence of LPT itself is predictive of risk for other asbestos-related diseases, including asbestosis, mesothelioma and lung cancer, a point that the EPA should include."

Carrie A. Redlich, MD, MPH
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APPENDIX C – 18

EXCERPTS

In The Matter Of :

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
SCIENCE ADVISORY BOARD

LIBBY AMPHIBOLE ASBESTOS REVIEW PANEL MEETING - DAY 1

February 6, 2012

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

SCIENCE ADVISORY BOARD

LIBBY AMPHIBOLE ASBESTOS REVIEW PANEL MEETING

DAY 1

Monday, February 6, 2012

(Transcript with Revised Corrections After Review of Counsel, July 2012)

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DR. WOSKIE: I have to remind you that my training is as an industrial hygienist, not a respiratory physician. So I have to defer to my colleagues' knowledge about the physiology. But the argument I thought was well made in the document and made sense to me and also was supported by the reported latency results that the localized pleural thickening occurs in, you know, 8, 10 years compared to the diffuse as far as follow-up, you know, having a cohort with sufficient follow-up to actually see disease.

So that was the other piece of the argument that made sense to me.

DR. KANE: Dr. Sheppard?

DR. SHEPPARD: Yeah, I generally also agreed. I brought up a question this morning and I want to revisit it and engage our physician colleagues on the panel with a little bit more discussion.

I think I've been convinced, but the basis in this data set is x-ray findings. And there are other changes on x-rays besides localized pleural thickening which are also caused by asbestos. And so

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as a statistician why not just look at all of them, any change on x-ray that might be caused -- that's considered caused by x-ray, I mean, by asbestos, particularly since these are prevalent x-rays.

And the changes most likely happened way back in time. So we are not looking at any time to event in this analysis at all. So I just wanted to revisit that question one more time before we put it to bed. Why -- and in fact in the primary analysis cohort it makes almost no difference because there's one case that's excluded that has another outcome. But in the bigger cohort there are more cases.

So why not help me understand a little bit better why wouldn't we look at more -- more changes on x-rays than just that one?

DR. KANE: Can anyone answer that question? Dr. Newman.

DR. NEWMAN: Well, I may not answer it, but I'll try. And I'll welcome input from some of my colleague pulmonologists. I think that's a really interesting idea.

As a general observation, the pleural

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findings will appear before the other findings. And so I think that's why the thinking has tended to focus on the pleural abnormalities.

DR. SHEPPARD: But my understanding is that sometimes you see the one outcome and not the other, right?

DR. NEWMAN: That's true. One can see, for example, asbestosis, the fibrotic lung disease, you can that on x-ray and in an individual who never develops any pleural abnormalities. So that definitely does occur.

DR. BALMES: I guess I'll just chime in as another pulmonary physician that again I think it's an interesting idea. I agree with Lee that usually you'll see localized pleural thickening before you would see asbestosis or diffuse pleural thickening.

The advantage of diffuse pleural thickening or asbestos is those are clearly linked to decreased lung function where localized or pleural thickening has been brought up isn't necessarily associated with decreased lung function. I don't know how much difference it would make with the Marysville cohort,

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but it's certainly a reasonable suggestion.

DR. KANE: Dr. Redlich, I would like to ask another pulmonologist.

DR. REDLICH: I think we would all sort of feel more comfortable because of this question of how significant our pleural plaques is if there was enough data to do a risk estimate on other outcomes, but in that same paper there were only 12 participants, I believe, or 8 with interstitial changes.

So it ends unbeing a much smaller number. And of the 80 with pleural changes, only 12 had diffuse pleural thickening. So -- what number was it? Did I have it wrong?

I am sorry. Even less. So I think the problem is there haven't been enough of those other endpoints.

DR. SHEPPARD: Yeah, but I'm talking about adding them all together, not looking at one outcome versus another.

DR. WOSKIE: So you are saying any --

DR. SHEPPARD: Yeah, any change.

DR. KANE: Yes, Dr. Salmon.

APPENDIX C – 19

EXCERPTS

In The Matter Of:

U.S. EPA - SCIENCE ADVISORY BOARD - LIBBY ASBESTOS REVIEW PANEL MEETING

July 25, 2012

MEETING (U.S. EPA - SCIENCE ADVISORY BOARD LIBBY ASBESTOS) - Vol. 1

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

SCIENCE ADVISORY BOARD

LIBBY AMPHIBOLE ASBESTOS REVIEW PANEL MEETING

Meeting Via Teleconference

Wednesday, July 25, 2012

1:00 p.m.

(Includes Revisions Amended By Counsel

as of September 17, 2012)

The U.S. Environmental Protection Agency, Science Advisory Board, Libby Asbestos Meeting held via teleconference on Wednesday, July 25, 2012, commencing at 1:00 p.m., reported stenographically by Elizabeth Mingione, Registered Professional Reporter and Notary Public for the State of Maryland, Commonwealth of Virginia, and the District of Columbia.

Job No.: 1-218474
Reported By: Elizabeth Mingione, RPR
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PROCEEDINGS

DR. WONG: I think we can start right now. According to my records, the panel members present for this conference call include Dr. James Bonner, Mr. John Harris, Dr. Hei, Dr. Kriebel, Dr. Lippmann, Dr. Neuberger, Dr. Newman, Dr. Pennell, Dr. Rutledge, Dr. Salmon, Dr. Sheppard, Dr. Southard and Dr. Walker. Did I miss anyone?

And of course we have our Chair also, Dr. Agnes Kane. Did I miss anyone?

DR. GUTHRIE: George Guthrie just joined in.

DR. WONG: Thank you. Who else?

DR. WEBBER: Jim Webber.

DR. WONG: Thank you. And who else?

DR. WOSKIE: Susan Woskie.

DR. WONG: Oh, great. Okay. Okay. We can start.

INTRODUCTORY REMARKS

DR. WONG: Good afternoon. I am Diana Wong, the Designated Federal Officer or DFO for the Science Advisory Board, Libby Amphibole Asbestos

Review Panel. I would like to convene this public teleconference of the panel.

Before we start today's discussion, I would like to provide a short statement concerning the Federal Advisory Committee Act. The SAB Libby Amphibole Asbestos Review Panel is a Federal Advisory Committee. And by EPA policy it's meetings and deliberations are held as public meetings that meet the requirements of the Federal Advisory Committee Act also known as FACA.

Through the charter, Science Advisory Board the panel is empowered by law to provide advice to the administrator. Consistent with the requirements of FACA and with EPA policy, the deliberations of the panel are conducted in public at meetings for if and when public notice is given. The discussions and substantive deliberations of the panel, its interactions with the public and the agency are conducted in sections where I as the DFO am present to ensure that the requirements of FACA are met.

And this includes the requirements for open meetings, for maintaining records of deliberation of the panel, making available to the public summaries of meetings, and provide opportunities for public comment. I would like to note that four members of the public have asked to make their own statements. And there is time on the agenda of this teleconference to hear public comments.

I have received three sets of written comments from the public for the panel's consideration. These comments and other meeting materials have been posted on the SAB web site. And I also want to note that the status of this panel's compliance of the federal ethics law, the SAB staff office have determined that there are no conflict of interest or appearance of a lack of impartiality issues for any of the advisory committee members.

After this teleconference, minutes will be prepared to summarize discussions and action items, an accordance requirement of FACA. And these minutes will be certified by the panel chair once completed.

I have already noted the names of the SAB panel members participating. We will not ask representatives of EPA or members of the public to

identify themselves. I will include in the minutes a list of those who directly request the call-in number for this teleconference. If there are others who would like to have the name included in the minutes, please send me an e-mail.

And i would also like to mention one other point. This is a large conference call, so please put your phone on mute by pressing star 6 when you are speaking. To unmute, press pound 6.

And now I would like to turn the call over to Dr. Agnes Kane, Chair of the SAB Libby Amphibole Asbestos Review Panel to review the agenda and begin the teleconference. Dr. Kane. Dr. Kane?

DR. KANE: Can you hear me?

DR. WONG: Yes, I can hear you.

MEETING COMMENCES, CHAIRED BY DR. AGNES KANE

DR. KANE: Okay. Good. Thank you very much, Diana, for organizing this. And I would like to thank in advance the members of the panel and also acknowledge their hard work in revising this draft document that we are going to be discussing today.

We have a lot to cover this afternoon. And

we will first hear remarks from the EPA followed by the public comments which are limited to three minutes for each presenter, followed by any questions that the panel will have for each speaker.

Then we will turn to the discussion of our draft report beginning with Section 3.2.5, inhalation reference concentration. The major changes that were involved in this draft are focused on the section. And many of the outside comments as well as questions from EPA deal with this section.

And this will probably occupy our discussion for most of the afternoon. Then we will review the Executive Summary, the letter to the Administrator, followed by a review of other sections.

Are there any questions? Okay. At this point I would like to ask Mr. David Bussard from EPA to summarize their remarks.

PRESENTATION BY DAVID BUSSARD

DR. BUSSARD: Thank you, Dr. Kane. First of all, again, our appreciation of the time and attention. We can see the drafts converging and appreciate clarifications that have already been made.

The whole team looked at the draft report and we have a couple things to raise, some of which are kind of nuances of wording and consistency. So you may pick them up as you go through making sure all the parts are consistent. And a few which I'll flag were really -- in some cases not quite sure how to implement a recommendation as we read it.

I'll try to go through these quickly. I do think the first topic on your agenda is one of the areas where we have the most interest in hearing the discussions and clarifications, so I would not want to divert you from the agenda that you have got.

The first issue is probably one of in part consistency of wording across pieces. We got music for a minute there. Okay. And I think it's explanatory, but it has to do with just being clear whether the panel has a view on whether LPT is adverse on its own, whether it's adverse as a predictor --

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(Music is playing on the phone call)

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DR. BUSSARD: -- is a predictor, is it a

predictor controlling for exposure or without --

DR. WONG: Excuse me. I need to interrupt. Please put your line on mute by pressing star 6 if you are not speaking because we can hear music.

We can still hear the music. Okay. Sorry for the interruption, Dave. Just go on.

DR. BUSSARD: No. That's fine. It was distracting. I appreciate that.

So the first issue is just wanting to be clear from the committee if you have got a view as to whether LPT is adverse on its own, whether it impairs lung function, whether it's predictive, controlling for exposure, or predictive but not controlling for exposure. And if you think it's predictive controlling for exposure, it would be really helpful to highlight particular references that you would cite that would support that.

Issue 3, and I appreciate there's already been some response to that, we think we captured the information that's available on fiber characteristics study by study in Appendix D. If that's not the case, we'd love to know that and get additional information.

From there I think we can have discussion about how much to put in the body of the text and how much to put in the appendix. We'd particularly like to know if we've missed some information that would be available study by study.

Issue 4, I think we understand what the panel is recommending in terms of allowing for TSFE to affect the slope and fixing the plateau instead. What we would ask for is some thought or clarity about if even after we do all of that Michaelis-Menten is a better fit, a better relative fit.

Is there a reason that you would really tell us we just cannot use that? And we raise this because at least with some of the past modeling that we didn't fix the plateau, my recollection is the Michaelis-Menten was a much better fit for something like 50 AFC points. We don't know what will happen when we rewrite that.

And we get the idea of a broader set and keeping some things flexible, but it would be useful to clarify if at the end of the day that still was the best fit. Is there a reason it really should just be

off the table towards the point that we should look at a broader set of models.

Issue 5 is one that we would particularly love to hear some discussion today. And I think it tracks with your agenda item. We, as I understand it, and I'm really representing the team here, I think we kind of understand the principle of what's being suggested here but are not totally sure how to implement it.

If there get to be issues of a few (inaudible) model on the full set do you carry over the MRE estimate for things that affect that. Do you capture the -- the uncertainty in them. So we'd love some discussion about really practical advice or references or citations, examples is this -- how to implement this and deal with the things that come up. And we have folks that would be happy to answer questions earlier, more the kinds of questions we've got.

From the ones we labeled six and seven, I think we are -- we understand what the panel is getting at. We looked at the references that were

available and while there -- they help explain some things, we don't think it quite gets us to the point of understanding how to practically do this. The data that sometimes is missing lots of -- lots of data points are missing, unfortunately.

So we might want some acknowledgment that there may be difficulties doing this, and it may not be cut and dry how to do this with this kind of a data set. And, similarly, for using the forshay (sp) inequality approach, at least at this point we understand that as way to deal with probability information, but we are not sure how it folds into the process of actually -- (inaudible) -- possible statistical analysis coming up with confidence. So, again, some either recognition that that may be difficult or -- (audible).

So that's a fast walk through. We'd be happy at the appropriate time to resharpen the question or help in any way, but that's a quick walk through. But, again, great appreciation for what you have done really -- (inaudible) -- forward to getting the final report.

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DR. KANE: All right. Thank you, Mr. Bussard. We will be addressing your questions after we hear from our public commenters, specifically when we talk about the draft report. And if we omit anything, please do not hesitate to remind us.

At this point I would like to invite those members of the public who have signed up to present public comments. And the first speaker will be Dr. Elizabeth Anderson.

DR. ANDERSON: Thank you, Dr. Kane. Today I would like to refer to prior comments that I have made in my Comment Number 1, and coauthored with Dr. David Hoal in my Comment Number 2, and also point to comments made by Dr. John Desesso and Dr. Larry Moore who address specific issues that I have noted in the current draft.

The first of those issues is the choice of the critical endpoint. And the particular language is that localized pleural thickening is predictive of diffuse pleural thickening, asbestosis and lung cancer and is a risk factor for all three. The second language I noticed is that the structural alteration

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of the pleura is associated with reduced lung function.

I think the scientific content in the prior comments present some challenges to support scientific foundations for each statement. One question is whether these statements are necessary to support the choice available to a critical endpoint, that is if LPT is not a risk factor for a known predictor.

(Phone noises making speaker inaudible)

DR. ANDERSON: -- EBT, asbestosis and lung cancer are associated with lung function, would it still be selected as a critical endpoint.

EPA's comments address the issue that LPT is primarily a marker of exposure and can occur at various levels of exposure and is not associated with the levels of exposure necessary to induce diffuse pleural thickening, asbestosis and lung cancer. And it is not on a biological pathway to these endpoints. And by definition they found the parietal pleura and not the visceral pleura and, therefore, because of this anatomical location unlikely to impair lung function.

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The second point I noted in the current draft is the reference to the lung function deficit relationship to LPT. I think we have challenges here. I noted in my earlier report that the Marysville cohort when it was first published by Lockey in 1984 showed no association between lung function deficit and LPT.

The current database on Marysville data is currently lacking lung function data. These data are expected later this year. So I think it's compelling that we get these data in order to look at the association critically. As best I can tell, we have no single study that combines the ability to evaluate exposure, the occurrence of LPT and lung function deficit.

I note also with only ten cases of LPT and one subcohort of one study we have a very limited basis to support the derivation of the RfC. I point to the particular issue from a current draft because of the profound applications of the current level. And, as I noted, the current level is within background.

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In fact, it's at the lower end of background as described in the ATSDR document that places urban background at .00001 and rural at .00001. Also this level is -- it will become the risk driver. It's going to be the risk driver in all cases that the de minimus risk brings for 20 years of exposure or less at the 10-to-the-minus-6 level.

I also note that the sensitivity cancer end the large-scale measurements, when large volumes of air have been pulled through filters in Libby that this level is two times higher and had not been detected by the data. And I noted in this draft document the language that says that -- one second -- the specific language, "In considering other studies, the appropriate assumption is that LAA fibers have the same mechanisms of toxicity and quantitative risk relations as that of other asbestos fibers," which goes to the point that the draft RfC if adopted is likely to be applied broadly to all asbestos types.

I feel that there are many challenges for this RfC and particularly important in light of the current focus on EPA and the IRIS database. Thank you, Dr. Kane.

DR. KANE: Thank you, Dr. Anderson. Do members of the panel have any questions? Okay.

Our next public speaker will be Dr. Moolgavkar.

DR. MOOLGAVKAR: Thank you very much, Dr. Kane, for giving me this opportunity to speak today. And forgive me for being blunt, but I think the midnight hour is upon us; and this panel's report is still replete with loose and inaccurate statements. And I feel that it could come back to embarrass the panel at a later date.

So the first point that I want to touch on is related to the RfC. And it's the same point that Dr. Anderson has raised and Mr. Bussard talked about this morning. I don't perceive any evidence that pleural plaques are predictive of more serious lung disease or of pulmonary function deficits because there is no evidence that conditional on asbestos exposure that there's any association between pleural plaques and these more serious conditions.

And if the panel knows of good literature

supporting this position, they should let the agency know what this literature is. And I would like to know whether the panel has critically evaluated the papers that they are recommending to the agency on this particular topic.

The panel continues to make the ill-advised recommendation that all x-ray abnormalities be thrown together in a single analysis. This is analogous to saying that lung cancer and mesothelioma should be analyzed together for the cancer end. And I don't think that anyone should advocate that -- so this is a poor recommendation as I've been saying for quite some time.

The panel recommends also that the Dichotomous Hill model be used instead of Michaelis-Menten model. And I don't think there's any more biological justification for the Dichotomous Hill model and for the Michaelis-Menten model. In fact, it requires the estimation of four parameter -- one more than the number of parameters estimated for the Michaelis-Menten model.

And what the panel appears to be

recommending is that two of these parameters, the background rate and the plateau we get fixed at really what are highly uncertain values derived in populations that may not even remotely resemble the Marysville cohort. I cannot see any justification for doing so.

Then I want to talk just briefly about some issues arising in the derivation of the inhalation unit risk for cancer. With respect to lung cancer, the principal issue I think is the clear indication of effect modification by age, or in other words departures from proportionality of hazards in the Cox Proportional Hazards Model.

Instead of addressing the issue, the agency has swept it under the rug by choosing a small subcohort. And instead of talking about this issue which is really quite central to lung cancer risk assessment, the panel has actually wasted quite a bit of time talking about secondary or tertiary issues like whether mesothelioma and lung cancer endpoints are independent or not. That is really a non issue, a total non issue.

And, finally, in terms of inaccuracies, in several locations in the revised draft the panel refers to linearity of exposure response relationships for amphibole associated carcinogenesis and even suggesting that there is limited evidence to support said linearity. Well, this is really a loose statement; linearity of what?

What is the response they are talking about? What is the measure of exposure? If it's cumulative exposure, then there is no evidence of linearity. There are two mesothelioma models that we have: The Hodgson-Darnton model, which can be expressed in terms of cumulative exposure -- (inaudible) -- and that is nonlinear.

We have the Peto-Nicholson model, which cannot even be expressed in terms of cumulative exposure, that's linear in concentration but nonlinear in duration of exposure. So there's no linearity here.

The Cox model for lung cancer is log linear. It's not linear. Sometimes the excess relative risk model is used. The relative risk is modeled linearly in that case. However, that is an exception for lung cancer, and I do not believe that it will fit the data as well as the biologically based models such as the two-stage clonal expansion model.

Therefore, these loose statements should either be clarified in the draft or they should be removed. Thank you very much.

DR. KANE: Thank you, Dr. Moolgavkar. So far the public commenters have focused their discussion on LPT, localized pleural thickening, and the derivation of the RfC. And I believe that the last public commenter also will address this issue.

And so I would like the members of the panel to be considering specific responses about the LPT and perhaps an additional question for the public commenters after we hear from Dr. Hoal.

Are there any other questions for Dr. Moolgavkar? All right. I would like to ask the next speaker, Dr. Hoal to talk.

DR. HOAL: Thank you, Dr. Kane. First thing I have to say has pretty much been said, but I would like to get back to the RfC and the use of the

LPT as a predictor of supposedly adverse effects. That I don't think has been established, and as such is purely a marker, I don't know how good it is, of exposure.

And that's how I thought about the good markers we have for ionize (ph) and radiation with dicentrics and rings on circulating lymphocytes. These are markers of exposure, but biologically cannot progress to the (inaudible) cells will divide. Hear?

DR. KANE: Yes.

DR. HOAL: Okay. Now, when it comes to the models, we keep talking about the Hill model and the Michaelis-Menten model which are specific biological models. And I think they are -- they do not -- or I do not see how they apply to LPT. I am used to in modeling to have things like two-stage clonal expansion model in cancer or a multistage model in cancer and working off those models. Having a background and a plateau doesn't really make sense with the definitions of the Michaelis-Menten or the Hill model.

Now, if in fact we want some nonlinear

function, and we could just as well come up with any old nonlinear function or simple palm (ph) linear regression why there would be a plateau at a particular level. To me that implies then certain individuals are immune no matter what the duration or propensity of the exposure is. And, therefore, this is not clear at all how one should be using a plateau less than 100 percent.

I didn't see much in the way of discussion of BMIs and subpleural fat which can be misdiagnosed as pleural plaques, at least using radiographic film as opposed to CT scans. And of course BMI is also a risk factor for reduced pulmonary function. So you may have some problems there.

And, finally, I am surprised that we have a single small data set is being used to develop a RfC or an RFD or whatever you want. These are usually -- if you look at a number of animal studies or a number of epidemiological studies, you go through your calculation of NOAELs and come up with your RfCs and compare them and may end up selecting the value coming from this, but particular data set as the best but at

least see the dependency of the various data sets and the various models that can be used.

And I say I agree with the comments that Dr. Moolgavkar made in his statement about the cancer risk modeling and also Dr. Anderson's general comments. Thank you.

DR. KANE: Thank you. Do members of the panel have a question? Is Dr. Jay Flynn available?

DR. FLYNN: Yes.

DR. KANE: You may present now.

DR. FLYNN: Thank you. I'm Jay Flynn, medical director of the Libby Medical Program.

My initial comments concern the American Thoracic Society ATS document entitled Diagnosis and Initial Management of Non-malignant Disease Related to Asbestos. This was published in September 2004 in the ATS Journal.

EPA and SAB are relying on the ATS document to justify the selection of LPT or pleural plaques as an appropriate endpoint for the derivation of RfC. A paragraph on page 705 of this ATS document addresses the issue regarding the effects of pleural plaques on

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lung function.

The initial part of this paragraph suggests pleural plaques can cause a reduction of five percent or a loss of 140 MLs of FVC. The paragraph then goes on to state this has been a consistent -- this has not been a consistent finding. And longitudinal studies have not shown a more rapid decrement in pulmonary function in subjects with pleural plaques. Three references are cited.

The paragraph then says, Decrements when they occur are probably related to subclinical fibrosis. In other words, the decrements in pulmonary function are not due to LPT or pleural plaques. The paragraph concludes: Even so, most people with pleural plaques alone have well-preserved lung function.

The ATS document cites studies that support the hypothesis pleural plaques cause loss of pulmonary function. However, it also cites studies that provide the opposite point of view. Conclusion is that clearly these findings are scientifically inconsistent and should not be used to derive the RfC.

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I would next like to comment on the study Lung Function Radiographic Changes and Exposure Analysis of ATSDR data from Libby, Montana, USA, published in the European Respiratory Journal 2011 by D. Weil et al.

In this paper, Weil et al. reviewed the ATSDR B Reader reports from the medical testing program in Libby, Montana from 2000 and 2001. 482 participants were identified as having a pleural abnormality on PA chest x-rays by two out of three B Readers. The BMI of this group was 30.3, indicating obesity. The FVC percent predicted was 95.63 percent, which falls well within the normal range.

In the discussion of the paper, the following statements are made: Second paragraph, page 382, "Our review of the ATSDR data does not support the conclusion that pleural changes are associated with clinically significant reduced lung function."

Last paragraph on 382 states, "There was an expected detrimental effect on lung function due to cigarette smoking." Page 383, number 3 states, "With regard to the effect of pleural plaques on FEC in

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males, there was a small probably clinically insignificant reduction of 4.5 percent." Conclusion is that the decrease in FEC is most likely due to obesity and smoking and is not related to previous asbestos exposure.

My concluding comments are pleural plaques are merely markers of previous asbestos exposure and are not a disease pathway to adverse effects or directly cause adverse effects. The SAB panel should revise its opinion that LPT or pleural plaques are an appropriate endpoint to derive the RfC because the scientific literature does not support this position.

At the EPA teleconference on May 1, 2012, Dr. Lawrence Moore, a highly respected pulmonologist, presented public comments and submitted written comments entitled "Clinical Background Information and Comments on Recent Scientific Publications." And the draft EPA report, August 2011 -- (phone beeps) -- pointing to Libby amphibole asbestos.

Dr. Moore's comments provided excellent review of pleural plaques including their clinical effects as well as a review of several pertinent

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papers that the SAB panel may be considering. All members of the SAB panel are urged to review Dr. Moore's paper. Thank you.

DR. KANE: Thank you. All right. At this time does the panel have any questions specifically for Dr. Flynn? As most of these speakers are focusing their comments on LPT, I would like to ask members of the panel who have special expertise in this area to consider these.

Specifically did Drs. Newman or Redlich have something to add to this?

DR. NEWMAN: This is Lee Newman. Can you hear me?

DR. KANE: Yes.

DR. NEWMAN: Oh, good. I wasn't sure if I had the mute on. Yeah. No, I appreciate the comments that have been made today, and I've read the materials that were submitted as well.

We actually spent quite a bit of time going through this literature, and we also spent that time as a group discussing this. I understand that there are people who would have some points of disagreement around some of this literature, but I think the sum of it leads me the two conclusions: One, the statements that we've made as far as using the LPT as the endpoint are appropriate.

The one thing that I would consider us discussing further as a group here is the use of the word predictive. It sounds like people have gotten hung up on that term. And, you know, I think we could have a little discussion around whether we should use that term or use a term such as "associated with" as opposed to "predictive" when it comes to discussing the relationship of the localized pleural thickening to other asbestos-related endpoints. But otherwise I wouldn't be recommending any other changes in the document.

DR. KANE: Thank you, Dr. Newman. We will be discussing that in more detail when we get to that specific question from EPA.

Dr. Redlich?

DR. REDLICH: Yes. Carrie Redlich. I agree with Lee Newman.

DR. KANE: All right. As a panel member,

not the chair, I would also like to offer my opinion. I am a board-certified anatomic pathologist. And when I am confronted with a patient at autopsy or a lung biopsy specimen or a lung resection specimen, the presence of pleural plaques would be listed on my pathologic anatomic diagnoses. It is a pathologic abnormality.

DR. REDLICH: I would just add one other comment. I think part of this confusion relates to the difference between a clinical practice and epidemiology studies and what we consider, you know, an endpoint such that -- (inaudible) -- a biologically relevant endpoint even if it is not favorable or is not -- because that question has been asked. And so the comments that it usually is not associated with severe -- I don't believe the severity of the lung abuse (ph). I think the question is is it a relevant health endpoint.

DR. KANE: Thank you, Dr. Redlich. Do other members of the panel have any thoughts on this issue?

DR. SALMON: This is Andy Salmon here. I

think one of the things that we really need to keep in mind in this discussion is the point that was just made that, you know, this is an adverse pathological change which is -- (inaudible) -- observable. And from a public health point of view it's objectionable in its own right because of that.

You know if you ask the average person in the street is it all right for you to have these pathological changes in your body, they would probably say, no, it isn't. And that is the basis for the risk assessment that it's an adverse effect in its own right. Whether it has mechanistic implications or whether it has associations or predictions or other effects is an interesting question from the scientific and clinical points of view. But from the risk assessment points of view I think we need to simply say that, you know, this is a wonderful discussion to have, but the bottom line is we are looking at an adverse pathological change, and that that is -- because that is adverse and clinically observable, it's an appropriate endpoint to use for the risk assessment purpose.

And the, you know, the question about mechanisms and clinical outcomes and whether it's associated or predicted, I mean, as an aside I will say I prefer the word "associated" because it doesn't make an assertion which we don't actually need to make in order to achieve the risk assessment process that we are aiming for.

So, anyway, I --

DR. REDLICH: I agree with all of that.

DR. MOOLGAVKAR: Can I respond to that, Dr. Kane?

DR. KANE: Yes.

DR. MOOLGAVKAR: If that is the way --

DR. KANE: Please identify yourself.

DR. MOOLGAVKAR: Yes. This is Dr. Moolgavkar. If that is the way the panel feels, then it should clearly state that. That is not what the current report reads.

It says it's predictive. And that has quite a different meaning than saying that it by itself is a pathological endpoint and we are taking that into consideration when we derive an RfC based on

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that.

I think that should be clearly stated. I don't think that the panel should be making these kinds of loose scientific statements about predictions.

DR. KANE: I think -- I think I would like to clarify something, that this is not a loose use of a term. I think that we have a problem here and that the panel is a group of experts from many different fields. And the word predictive means something different in an epidemiologic context than it would in a clinical context.

And we will be discussing very shortly about whether we should change "predictive" to "associated with," as that is one of the purposes why we are having this conference call to make final recommendations and changes in the draft document. So we will be considering that change in great detail very shortly. Thank you.

Does any other members of the panel have any comments or questions? Mr. Bussard? Do you have any specific comments or questions at this point?

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DR. BUSSARD: I am good. Thank you.

DR. KANE: Okay. We will be addressing EPA specific remarks very shortly. All right. If there are no more questions or comments, at this point I would like to thank the public speakers, the public commenters, and we will now return to the panel's draft -- discussion of the draft report.

We are going to begin with the section which has where there were little substantive changes were made earlier, Section 3.2.5 on the RfC. And in our deliberations this afternoon, because we have a lot to discuss, I would like to advise the panel to only consider major changes in the wording.

If there are only very simple typographical errors, they will be corrected. We've received some of your written comments, but we will be discussing substantive changes, and particularly focusing on questions where the EPA raised points for clarification as specific questions.

So we will start now on -- see what the question is here -- all right. We'll start on page 25. This is Section 3.2.5.1. And there were several

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charge questions under this section. And specifically the panel in our revisions made several changes. All right.

So before we get to that, I am going to return to the issue on page 19. And that was the issue on localized pleural thickening as the critical effect for derivation of the RfC. After this point is the time to ask the panel members to consider how we worded this in terms of using the terms "predictive" versus "associated with". And can we reach a consensus on whether we should edit this to use one term versus the other?

DR. NEWMAN: This is Lee Newman. Can you hear me?

DR. KANE: Yes.

DR. NEWMAN: Yes. I would propose that we change it from the word "predictive" to "associated with" and just put that on the table here. I think that Dr. Salmon's point is well-taken one, that we don't actually need that to make the -- in fact help support the case that EPA has made for using this as our endpoint.

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And so I think that's just a nice way of taking that away as, you know, it's sort of an unnecessary sideline issue that we can change by changing to the words "associated with".

DR. KANE: All right. Do other members of the panel have questions, comments?

DR. BONNER: This is Jamie Bonner. Can you hear me?

DR. KANE: Yes.

DR. BONNER: I would just second Lee's recommendation.

DR. KANE: Excellent. Any other alternate suggestions, questions from members of the panel?

DR. PETO: This is Julian Peto. Can you hear me?

DR. KANE: Yes, hello.

DR. PETO: Oh, hi. I wonder, I mean, as this is such a major issue which people have been so critical of and nobody's challenging the assertion that there isn't actually scientific evidence of substantial cause and effect, I do agree with, I mean, Dr. Moolgavkar's point that if that's what we are

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saying we should be explicit about it I think is a fair one.

And I just wonder whether how much difference it would make. I mean how difficult would it be for the EPA to base an RfC on the cancer endpoint and say that we feel that this is a substantial pathological change in its own right. And so the RfC's been calculated on that basis. But it would be possible to calculate an RfC on the basis of cancer alone and that would be the alternative value.

I mean that would seem a reasonable compromise because I do rather feel that, I mean, they have made quite a strong case that we were asserting something that wasn't scientifically supported. And to deal with it by changing predictive to associated without being absolutely explicit about what we are doing and why we are doing it seems rather satisfactory.

DR. SALMON: Andy Salmon here. I don't think that we have been unclear about the view that the LPT is an adverse endpoint in its own right and that that was an appropriate basis of an RfC. I think

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the unfortunate implication that we were saying something other than that is something which has been sort of corrected by imputation rather than anything that we intended to imply at any point.

And I think to some extent the critics of the proposed RfC have seized on this as an obvious point of confusion or weakness, but it's not one that was present in our original discussions to my recollection.

DR. KANE: Thank you.

DR. PETO: Is it the case that other RfCs have been based on science as distinct from symptoms? I mean if the -- I mean, you know, don't get into a great long semantic argument but, I mean, if it's a clinical sign which is detectable by an examination but it doesn't have health consequences in the in the normal sense.

DR. SALMON: This is risk assessment not clinical medicine. And one of the --

DR. PETO: Just to be clear about, I mean, if it really is driving the RfC then what's a very clear statement about what --

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DR. SALMON: There's a fairly clear statement in a number of documents about really the appropriate methodology for non-cancer risk assessment, including specification of degrees of severity and effect. And one of the critical things which is looked for is indicating that the clearly adverse effect is an irreversible pathological change in the structure of an organ or organ system.

And this clearly qualifies as that. It meets the criteria which are used in risk assessment for definition of an adverse effect in its own right. And that is entirely consistent with what has been done in other context in risk assessment.

Now, there are a lot of interesting questions around the clinical significance of this and how -- the degree to which it's associated with -- may progress to or otherwise be related to other endpoints, but those are not questions which we necessarily have the information to answer in this specific context. And my point is that we don't need to, and we haven't said that we need to.

DR. PETO: But do you think the suggestion

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that it would be useful to say if the RfC based on cancer would be, do you think it would be inappropriate to put that in?

DR. NEWMAN: This is Lee Newman. I don't think that that's an appropriate direction to go at this time, to answer your question. It's, you know, certainly the people who have provided comments have done their best to make the case that there is some clinical dispute here in the literature.

In fact, I think the literature stands and our review of it stands, that this -- that the localized pleural thickening is an adverse and critical effect. And so I don't think that we need to go on the path of suggesting that we need an alternative such as cancer.

DR. KANE: Does EPA have any comments on this?

MALE SPEAKER: I think you are in the right track that what we are looking for is guidance is it an adverse effect in and of itself, and then being careful that if you make statements about it being predictive or associated with something else, that

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that be a separate statement so that these things are sort of sequentially clear. Is it an adverse effect in and of itself.

Do I make a statement about whether it's associated with other effects. But to sort of make those two separate questions is very helpful.

DR. VU: All right. Agnes, this is Vanessa. May I provide some information?

DR. KANE: Yes.

DR. VU: So the agency's derived the reference concentration for non-cancer health endpoints and what Julian, when you raised the point of whether the agency should consider an RfC for cancer, so the agency's general process for assessing cancer risk is use what -- is considering the method to develop the inhalation cancer unit risk. And the RfC is mainly for the non-cancer health end points. So I just hope that's clear.

DR. KANE: Thank you, Vanessa. I that helps I think clarify that point.

DR. HEI: So, Agnes? This is Tom from Columbia University.

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DR. KANE: Yes.

DR. HEI: I think Vanessa clarified the issues, and based on the discussion that we have. It is perhaps a little unfortunate to choose a word predictive which by itself has implication for a mechanistic or pathological pathway which at the moment that doesn't want seem to support that.

So the words "associate with" tends to bypass all these complications and put us back on the right track. So I think that the previous suggestion to remove that and change the words and probably will be very helpful at this moment.

DR. KANE: Thank you, Tom. Any other members of the panel have any comments at this point?

DR. SHEPPARD: Yeah. This is Lianne Sheppard. Following up on this discussion on line 23 of page 19, it may be helpful to EPA if we had a sentence that says something to the effect of this is an adverse effect in and of itself, just to be completely clear. Maybe the wording could be enhanced to recognize the risk assessment aspect of that definition.

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DR. KANE: Do members of the panel --

UNIDENTIFIED MALE SPEAKER: I think clarity on that would be very helpful, I would agree.

DR. NEWMAN: So this is Lee Newman. You are suggesting something stronger than what's on page 19, line 13, where it says, radiographic evidence of localized pleural thickening in humans is the appropriate adverse and critical effect for the derivation of the RfC; you want to add something else right after that? Is that what you are saying.

DR. SHEPPARD: No. I was suggesting because the paragraph people seem to be struggling with is the next one where that issue is brought up again, but then it goes on to talk about how it's related to the other health outcomes, and that seems to be getting blended in a way that seems to be causing problems.

And so basically taking that, you know, taking some version of that, of what's said on line 13 and inserting it there on line 23 might help with making that distinction. So it -- what I'm understanding from this conversation, there's two

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points.

One is that it's an averse effect for in and of itself because of the way risk assessment is defined and the pathological changes. And then in addition it's associated with other health outcomes. And -- and I -- my understanding is those are being blended in a way that's kind of the message is being misinterpreted.

DR. REDLICH: Yes. This is Carrie Redlich. I think we are all pretty clear. I think for time's sake we could quickly edit this second paragraph.

DR. KANE: All right, Carrie. You want to give that a shot?

DR. REDLICH: Yes. But rather not with this group on the phone.

DR. KANE: I agree with you, but I think we all understand, at least I think from the members of the panel and from my point of view I understand what the issues are. And so Carrie will work and try to clarify the sentence on page -- on line 23, LPT is a structural pathological alteration of the pleura.

Perhaps somewhere in there saying a adverse effect.

And then the lines 25 and 26 that talk about the association of LPT with other asbestos-related diseases as it's listed. And I think throughout this document and also as the EPA requested in its question number 1 in the letter to the administrator, the Executive Summary and any other place in the document, we should replace the word "predictive" with "associated with".

And I think that should clarify this issue. Is that clear to members of the panel? Any other questions or suggestions?

DR. HEI: I thought it's pretty fair.

DR. KANE: Okay. So, Carrie, you have an action item there. And I'm sure that we can clarify this. And I think these were very important points.

I'm glad that EPA brought it to our attention, the confusion by using these terms. Mr. Bussard, is that clear also.

DR. BUSSARD: I think we are clear. Thank you.

DR. KANE: Excellent. Excellent. All

right. So that takes care of that item.

All right. Now, we'll go back to Section 3.2.5 beginning on page 25. There were significant changes in the panel's draft with respect to questions 1, 2, 3, 4 and 6.

So do any members of the panel have -- any of your review have you found any substantive issues that need further discussion or modification?

DR. SHEPPARD: Are we going to go through these line by line or do you want us just -- I mean question by question? Because we should probably make sure that we respond to these specific items that EPA addressed.

DR. KANE: That's what I was coming to next. We are not going to go through it line by line. I expect that members of the panel have reviewed this draft document and reviewed our changes. And --

DR. SHEPPARD: I'm sorry. I meant question by question.

DR. KANE: Right. Question by question. We can do that if you wish but if have, you know, if people have done this, their homework and have no

problems with it, I think we can deal with it that way. And then we'll ask EPA or refer to EPA's questions specifically because that's the most important consideration here.

DR. SHEPPARD: I think we need discussion about their items number 4 and 5. And there may need to be some changes as a result of those.

DR. KANE: Yes. Right now we are on, yes, we'll be moving to those shortly after we are covering this section.

DR. SHEPPARD: Okay.

DR. KANE: Okay. So before we get to your questions four and five, Mr. Bussard, do you have any other questions on this section, particularly with respect to charge questions 1, 2, 3, 4 rand 6?

MR. BUSSARD: Other than the questions we have that articulate the question 3 -- I mean and the pages cited 28 through 31 or so, no. Thank you.

DR. KANE: Okay. Okay. Excellent.

DR. LIPPMANN: Mort here. Are you going to go to Issue 3?

DR. KANE: Yes, we will, but we'll do that

after we are done with the RfC and IUR.

DR. LIPPMANN: Okay.

DR. KANE: Don't worry. We are not forgetting you, because some members of the panel cannot stay through the whole conference call. And these are the most substantive changes in the document.

All right. So there is a question now that we can deal with. There seems to be a question, a response to Question 1. There's some confusion, a little bit of confusion about the use of arithmetic -- geometric means versus arithmetic means. And in -- Jason (?), do you have any comments on that one, Question 1A and 1B?

UNIDENTIFIED FEMALE: I didn't -- what -- I'm not picking up where the confusion is. I didn't see that in the EPA notes. I thought the panel had discussed this and concluded what the -- with what the current draft. Oh, I'm --

DR. KANE: Diana, can you help us with this? Where specifically does this issue come up?

DR. WONG: Well, you are referring to the

APPENDIX C – 20

DATE

EPA-SAB...

The Honorable Lisa P. Jackson
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460

Subject: Review of EPA's Draft Assessment entitled *Toxicological Review of Libby Amphibole Asbestos* (August 2011)

Dear Administrator Jackson:

EPA's Office of Research and Development (ORD) requested the Science Advisory Board (SAB) to conduct a peer review of EPA's draft Integrated Risk Information System (IRIS) assessment, entitled *Toxicological Review of Libby Amphibole Asbestos (August 2011)*. The draft document is the first IRIS assessment specific to Libby Amphibole asbestos (LAA), a term used to refer to the mixture of amphibole mineral fibers of varying elemental composition that have been identified in the Rainy Creek complex near Libby, MT. In response to ORD's request, the SAB convened an expert panel to conduct this review. The SAB Panel was asked to comment on the scientific soundness of the hazard and dose-response assessment of LAA-induced cancer and non-cancer health effects.

The SAB finds the EPA's draft assessment to be comprehensive and generally clear, logical, and well written. We have provided recommendations to further enhance the clarity and strengthen the scientific basis for the conclusions presented. The SAB responses to the EPA's charge questions are detailed in the enclosed report. SAB major comments and recommendations are provided below:

- The SAB supports the derivation of an inhalation reference concentration (RfC) based on radiographic evidence of localized pleural thickening in an occupationally exposed Marysville OH cohort. The SAB finds the selection of the subcohort of 118 workers who began work in 1972 or later when exposure data were available and who had X-ray exams, with the full cohort of 434 workers used for confirmatory analyses to be clear and reasonable. However, the SAB finds that additional analyses are needed to strengthen and support the RfC. The SAB recommends that EPA include any X-ray abnormalities (localized pleural thickening, diffuse pleural thickening, or asbestosis) as the health outcome. The SAB also recommends that EPA conduct confirmatory analyses (to the extent data permit) of pleural abnormalities using the recently published studies on the Libby workers cohort and the Minneapolis Exfoliation community cohort.

- The SAB agrees that localized pleural thickening has the appropriate specificity, and has a measurable relationship to altered lung function, and is a structural pathologic alteration of the pleura. The presence of localized pleural thickening itself is predictive of risk for other asbestos-related diseases, including asbestosis, mesothelioma and lung cancer. The SAB has identified and provided the EPA with additional references and recommends that the agency to conduct a more detailed review of the literature to further support this conclusion.

- For exposure-response modeling of non-cancer endpoints, the SAB recommends that a clearer description be provided of how the "best" model was chosen. The SAB also recommends examining other exposure metrics besides the simple cumulative exposure, such as time weighting of exposures. In addition, more justification is needed for the selection of 10% extra risk as the benchmark response which is not consistent with EPA's guideline for epidemiological data.

- A composite uncertainty factor of 100 was applied to the point of departure to obtain the RfC. The SAB supports the intraspecies uncertainty factor of 10 to account for human variability and sensitive subpopulations. However, the SAB recommends that the EPA consider additional data and analysis for the application of a database uncertainty factor of 10.

- The SAB agrees that the weight of evidence for LAA supports the descriptor "Carcinogenic to Humans by the Inhalation Route", in accordance with EPA's *Guidelines for Carcinogen Risk Assessment*. The SABs also supports the EPA's conclusion that there is insufficient information to identify the mode of carcinogenic action of LAA, and therefore the default linear extrapolation at low doses is appropriate.

- The SAB supports the selection of the Libby worker cohort for the derivation of the inhalation unit risk (IUR) and agrees that the use of the subcohort post 1959 for quantification is reasonable due to the lack of exposure information for many of the earlier workers. The SAB finds the use of lung cancer and mesothelioma as endpoints to be appropriate for the derivation of the IUR. However, the SAB recommends a more detailed discussion on how the use of mortality data rather than incidence data may have resulted in an undercount of both cancer outcomes.

- The SAB agrees that the agency clearly described the methods they selected to conduct the exposure-response modeling for lung cancer and mesothelioma. However, the SAB suggests that the agency provide a broader justification for its choice of statistical models to characterize the exposure response function. The SAB recommends that the Agency evaluate the time dependence of disease by providing tabulation of mesothelioma mortality rates and lung cancer standardized mortality ratios by time since first exposure, duration of exposure, and period of first exposure for both the full and subcohort.

- There are several competing models- Weibull, and the two stage clonal expansion (TSCE) - that could have been used instead of or in addition to the Poisson and Cox models that might have provided very different estimates of risk, but these are not discussed in the document. Use of the TSCE model, for example, could allow for a more direct evaluation of, and possibly justification for, age-dependency of the IUR.

- The SAB believes the agency has been overly constrained by reliance on model fit statistics as the primary criterion for model selection. The SAB recommends graphical display of the fit to the data for both the main models and a broader range of models in the draft document to provide a more complete and transparent view of model fit.

- The EPA has summarized many sources of uncertainty, sometimes quantitatively, as well as the direction and magnitude of the likely impact of each source of uncertainty. However, the SAB identifies an important source of uncertainty, namely, model uncertainty, that might not be accounted for in the use of the 95% upper confidence limit on the inhalation unit risk (IUR) and the combined IUR. The SAB recommends that a more straightforward and transparent treatment of model uncertainty would be to estimate risks using a more complete set of plausible models for the exposure-response relationship, including the Cox and Poisson models. This sensitivity analysis, while not a full uncertainty analysis, would make explicit the implications of these key model choices.

The SAB appreciates the opportunity to provide the EPA with advice on this important subject. The SAB urges the agency to move expeditiously to finalize this IRIS document for Libby Amphibole Asbestos. We look forward to receiving the agency's response.

Sincerely,

believes additional analyses/cohorts are needed to strengthen and support the RfC. The SAB suggests that EPA include any X-ray abnormalities as the outcome (localized pleural thickening (LPT), diffuse pleural thickening (DPT), or asbestosis). The SAB also suggests that the EPA conduct analogous analyses (to the extent the data permit) of pleural abnormalities among the Libby workers cohort (Larson et al.,2012), and the Minneapolis Exfoliation Community cohort (Adgate et al.,2011; Alexander et al.,2012).

The SAB agrees that the radiographic evidence of localized pleural thickening (LPT) in humans is the appropriate adverse critical effect for the derivation of the RfC. LPT has the appropriate specificity and is not confounded by cigarette smoking. It is physiologically important due to its measurable relationship to altered lung function, and is a structural, pathologic alteration of the pleura. The reported findings are compatible with the animal data showing tissue injury and inflammation. Moreover, the presence of LPT itself is predictive of risk for other asbestos-related diseases, including asbestosis, mesothelioma and lung cancer, a point that the EPA should include as well. However, the SAB has identified additional relevant publications and a more detailed review of the literature is needed to further support this conclusion.

Use of Animal and Mechanistic Studies

In general, the SAB finds the laboratory animal studies listed in Tables 4-15, and 4-16 and summarized in Appendix D to be appropriate and complete. Laboratory animal studies using a variety of non-inhalation routes of exposure have been used to ascertain the potential fibrogenic and carcinogenic potential of the LA. While inhalation is regarded as the most physiologically relevant mean of fiber exposure in animals, there is no published study using this route of exposure in experimental animals. Therefore, the deposition of particles and fibers cannot be adequately addressed. However, inhalation studies have been conducted with tremolite. The relative potency of inhaled LAA should be compared with that of tremolite to add new information for refining the RfC for LAA.

Limited mechanistic studies using *in vitro* assay systems have utilized non-specific endpoints (e.g., pro-inflammatory cytokines, enzyme release and oxidative stress markers), and will probably not shed much light on the mechanisms of LAA-induced disease.

Carcinogenicity

Weight of Evidence Characterization

The SAB agrees that the weight of evidence for LAA supports the descriptor "Carcinogenic to Humans by the Inhalation Route", in accordance with EPA's *Guidelines for Carcinogen Risk Assessment* (USEPA,2005). The occupational studies showed dose-related increased risks of lung cancer and mesothelioma among workers exposed by inhalation, although the numbers of cases are small, particularly in the sub-cohort used from the Marysville, Ohio plant that had lower estimated levels of exposure. The case series in the community, while supportive, does not provide the same level of evidence for an association, or for the strength of the association. Effects from short term intra-tracheal instillation studies in mice and rats include altered gene expression, collagen induction, and inflammatory response, and are consistent with the early-stage pathological change induced by other

2. *Radiographic evidence of localized pleural thickening in humans was concluded by EPA to be an adverse effect and was selected as the critical effect for the derivation of the RfC. Pleural thickening is associated with restrictive lung function, breathlessness during exercise and, for some individuals, chronic chest pain. Please comment on whether the selection of this critical effect and its characterization is scientifically supported and clearly described. If a different health endpoint is recommended as the critical effect for deriving the RfC, please identify this effect and provide scientific support for this choice.*

The selection of radiographic evidence of localized pleural thickening (LPT) in humans is the appropriate adverse effect and critical effect for the derivation of the RfC. This is well supported by the lines of evidence presented in section 4.1.1.4.2. The section is scientifically supported and clearly described although, as described below, the SAB believes additional evidence is available and to further support this view and should be reported.

While other health endpoints might have been considered candidates for the critical effect for deriving the RfC, such as diffuse pleural thickening and small opacity profusion, none is superior to localized pleural thickening. LPT is found at a significantly elevated prevalence in the community of exposed individuals. Localized pleural thickening has the appropriate specificity and is not confounded by cigarette smoking. LPT is physiologically important due to its measurable relationship to altered lung function. LPT is a structural, pathologic alteration of the pleura. The findings reported in this section are compatible with the animal data showing tissue injury and inflammation. Additionally, the presence of LPT itself is predictive of risk for other asbestos-related diseases, including asbestosis, mesothelioma and lung cancer, a point that the EPA should include, as well. The SAB discussed that while it fully agrees with the merits of using LPT detected by chest radiograph and CT scan as the appropriate adverse effect and critical effect for the derivation of the RfC, this approach should not preclude EPA from using more sensitive diagnostic techniques that may identify earlier or more specific pleural changes in the future

.

Due to the landmark action of developing an RfC for LAA, the SAB discussed the need for the inclusion of a more detailed review of the literature to support the presence of a relationship between localized pleural thickening and both pathologic and physiologic abnormalities. There is additional literature that addresses and demonstrates the relationship between LPT and restrictive lung function that should be included. Published studies suggested by the SAB (Clin et al., 2011; Paris et al., 2009; Lilis et al., 1992) should be considered and include those referenced in the American Thoracic Society (ATS) Statement entitled, *Diagnosis and Initial Management of Nonmalignant Diseases Related to Asbestos: Official Statement of the American Thoracic Society*, (ATS,2004) (Miller et al., 1992; Miller, 2002; Schwartz et al., 1990; Jarvolm and Sanden, 1986; Hjortsberg et al., 1988; Oliver et al., 1988; Bourbeau et al., 1990; Ohlson et al., 1984; Ohlson et al., 1985; Sichletidis et al., 2006; Van Cleemput et al., 2001; Whitehouse (2004; Wilken et al., 2011). Consistent with that Statement, it is the view of the SAB that large cohort studies have shown a significant reduction in lung function, including diminished diffusing capacity and vital capacity attributable to LPT. The SAB also recommends that the EPA provide a more thorough review of the physiologic relationship between LPT found on chest x-ray and CT scan and lung function, not limiting itself to Libby amphibole asbestos.

The SAB also suggests that the EPA consider looking at LPT, DPT and small opacity profusion score together as an outcome. There is evidence that LPT is not always the first adverse effect that is detected

APPENDIX C – 21

EXCERPTS

Materials Submitted to the National Research Council
Part I: Status of Implementation of Recommendations

U.S. Environmental Protection Agency

Integrated Risk Information System Program

January 30, 2013

Table of Contents

I. Introduction

The U.S. Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS) Program develops human health assessments that provide health effects information on environmental chemicals to which the public may be exposed, providing a critical part of the scientific foundation for EPA's decisions to protect public health. In April 2011, the National Research Council (NRC), in their report *Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde*, made several recommendations to EPA for improving IRIS assessments and the IRIS Program. The NRC's recommendations were focused on Step 1 of the IRIS process, the development of draft assessments. Consistent with the advice of the NRC, the IRIS Program is implementing these recommendations using a phased approach and is making the most extensive changes to assessments that are in the earlier stages of the IRIS process.

Background on IRIS

IRIS human health assessments contain information that can be used to support the first two steps (hazard identification and dose-response analysis) of the risk assessment paradigm. IRIS assessments are scientific reports that provide information on a chemical's hazards and, when supported by available data, quantitative toxicity values for cancer and noncancer health effects. IRIS assessments are not regulations, but they provide a critical part of the scientific foundation for decisions to protect public health across EPA's programs and regions under an array of environmental laws (e.g., Clean Air Act, Safe Drinking Water Act, Comprehensive Environmental Response, Compensation, and Liability Act, etc). EPA's program and regional offices combine IRIS assessments with specific exposure information for a chemical. This information is used by EPA, together with other considerations (e.g., statutory and legal requirements, cost/benefit information, technological feasibility, and economic factors), to characterize the public health risks of environmental chemical and make risk management decisions, including regulations, to protect public health. IRIS assessments are also a resource for risk assessors and environmental and health professionals from state and local governments and other countries. Figure 1 illustrates where IRIS assessments contribute information within the risk assessment and risk management paradigms.

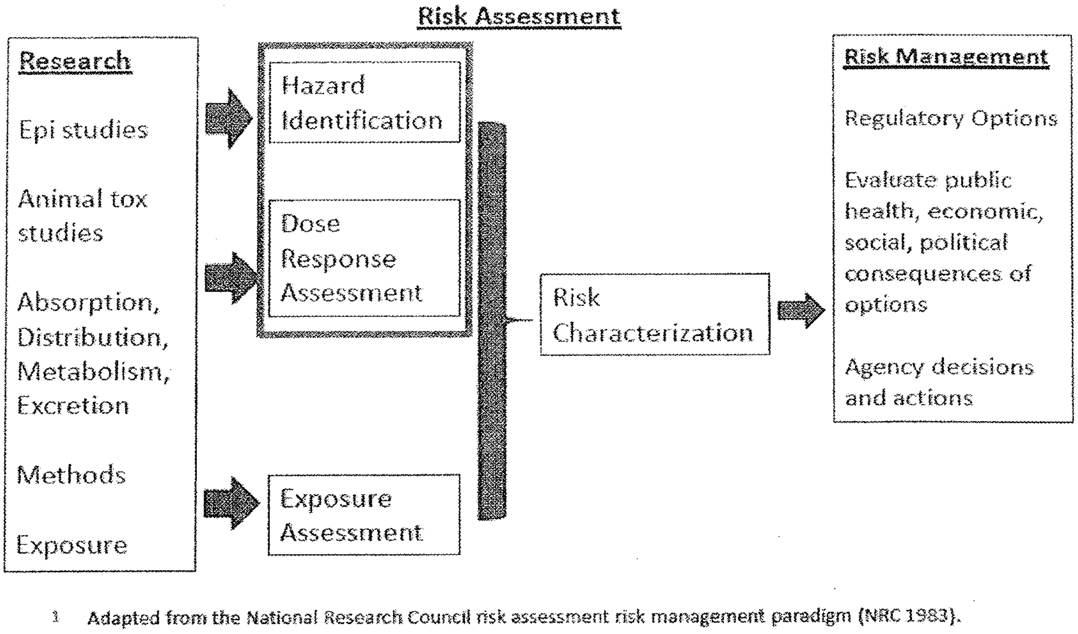

Figure 1. Risk Assessment Risk Management Paradigm (adapted from the National Research Council's paradigm, 1983). The red box shows the information included in IRIS assessments.

II. Charge to the NRC Expert Panel

In April 2012, EPA contracted with the NRC to conduct a comprehensive review of the IRIS assessment development process. The panel will review the IRIS process and the changes being made or planned by EPA and will recommend modifications or additional changes as appropriate to improve the process, and scientific and technical performance of the IRIS Program. The panel will focus on the development of IRIS assessments rather than the review process that follows draft development. In addition, the panel will review current methods for evidence-based reviews and recommend approaches for weighing scientific evidence for chemical hazard and dose-response assessments.

III. Overview of EPA's Implementation of NRC's Recommendations

EPA agrees with the NRC's 2011 recommendations for the development of IRIS assessments and plans to fully implement the recommendations consistent with the NRC panel's "Roadmap for Revision," which viewed the full implementation of their recommendations by the IRIS Program as a multi-year process. In response to the NRC's 2011 recommendations, the IRIS Program has made changes to streamline the assessment development process, improve transparency, and create efficiencies within the Program. The following sections outline the NRC's 2011 recommendations and provide an overview of how the IRIS Program is implementing the NRC's general and specific recommendations. changes that have been made and will be made in response to the recommendations are provided in Appendices to this report.

In addition, chemical-specific examples demonstrating how the IRIS Program is currently implementing the NRC's 2011 recommendations have also been provided to the panel (see additional document provided, *Chemical-Specific Examples Demonstrating Implementation of NRC's 2011 Recommendations*). The examples cover literature search and screening, evaluation and display of individual studies, development of evidence tables, evidence integration, selecting studies for derivation of toxicity values, dose-response modeling output, and considerations for selecting organ/system-specific or overall toxicity values. The examples are not to be construed as final Agency conclusions and are provided for the sole purpose of demonstrating how the IRIS Program is implementing the NRC recommendations.

NRC's General Recommendations and Guidance

NRC Recommendations[1]:

- To enhance the clarity of the document, the draft IRIS assessment needs rigorous editing to reduce the volume of text substantially and address redundancies and inconsistencies. Long descriptions of particular studies should be replaced with informative evidence tables. When study details are appropriate, they could be provided in appendices.
- Chapter 1 needs to be expanded to describe more fully the methods of the assessment, including a description of search strategies used to identify studies with the exclusion and inclusion criteria articulated and a better description of the outcomes of the searches and clear descriptions of the weight-of-evidence approaches used for the various noncancer outcomes. The committee emphasizes that it is not recommending the addition of long descriptions of EPA guidelines to the introduction, but rather clear concise statements of criteria used to exclude, include, and advance studies for derivation of the RfCs and unit risk estimates.
- Elaborate an overall, documented, and quality-controlled process for IRIS assessments.
- Ensure standardization of review and evaluation approaches among contributors and teams of contributors; for example, include standard approaches for reviews of various types of studies to ensure uniformity.
- Assess disciplinary structure of teams needed to conduct the assessments.

Implementation:

➢ **New Document Structure**

Implemented

In their report, the NRC recommended that the IRIS Program enhance the clarity of the document, reduce the volume of text, and address redundancies and inconsistencies. To improve the clarity of IRIS assessments, the IRIS Program has revised the assessment template to substantially reduce the volume of text and address redundancies and inconsistencies in assessments. The new template provides sections for the literature search strategy, study selection and evaluation, and methods used to develop the assessment.

[1] National Research Council, 2011. Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde.

➢ **Evidence Tables**

Implemented

The IRIS Program has developed templates for evidence tables to standardize the presentation of reviewed studies in IRIS assessments. Once a literature search has been conducted and the resulting database of studies has been evaluated, evidence tables are developed to present information from the collection of studies related to a specific outcome or endpoint of toxicity. The evidence tables include studies that have been judged adequate for hazard identification and display available study results, both positive and negative results. The studies that are considered to be most informative will depend on the extent and nature of the database for a given chemical, but may encompass a range of study designs and include epidemiology, toxicology, and, other toxicity data when appropriate.

For more detailed information, see "Reporting Study Results" in the Evaluation and Display of Individual Studies section in the draft Handbook for IRIS Assessment Development in Appendix F.

A chemical-specific example of the implementation of this recommendation is available as "EXAMPLE 3 – Evidence Tables" in the Chemical-specific Examples Demonstrating Implementation of NRC Recommendations document.

Weight-of-Evidence Evaluation: Integration of Evidence for Hazard Identification

NRC Recommendations:

- Strengthened, more integrative and more transparent discussions of weight of evidence are needed. The discussions would benefit from more rigorous and systematic coverage of the various determinants of weight of evidence, such as consistency.
- Review use of existing weight-of-evidence guidelines.
- Standardize approach to using weight-of-evidence guidelines.
- Conduct agency workshops on approaches to implementing weight-of-evidence guidelines.
- Develop uniform language to describe strength of evidence on noncancer effects.
- Expand and harmonize the approach for characterizing uncertainty and variability.
- To the extent possible, unify consideration of outcomes around common modes of action rather than considering multiple outcomes separately.

Implementation:

➢ **Integration of Evidence for Hazard Identification**

In Progress

The IRIS Program has strengthened and increased transparency in the weight-of-evidence for identifying hazards in IRIS assessments. Hazard identification involves the integration of evidence from human, animal, and mechanistic studies in order to draw conclusions about the hazards associated with exposure to a chemical. In general, IRIS assessments integrate evidence in the context of Hill (1965), which outlines aspects — such as consistency, strength, coherence, specificity, does-response, temporality, and biological plausibility — for consideration of causality in epidemiologic investigations that were later modified by others and extended to experimental studies (U.S. EPA, 2005a).

All results, both positive and negative, of potentially relevant studies that have been evaluated for quality are considered (U.S. EPA, 2002) to answer the fundamental question: "Does exposure to chemical X cause hazard Y?" This requires a critical weighing of the available evidence (U.S. EPA, 2005a; 1994), but is not to be interpreted as a simple tallying of the number of positive and negative studies (U.S. EPA, 2002). Hazards are identified by an informed, expert evaluation and integration of the human, animal, and mechanistic evidence streams.

For more detailed information, see "Synthesis of Observational Epidemiology Evidence", "Synthesis of Animal Toxicology Evidence", and "Mechanistic Considerations in Elucidating Adverse Outcome Pathways" in the Evaluating the Overall Evidence of Each Effect section in the draft Handbook for IRIS Assessment Development in Appendix F.

See also Section 5 ("Evaluating the overall evidence of each effect") in the Preamble to IRIS Toxicological Reviews in Appendix B.

A chemical-specific example of the implementation of this recommendation is available as "EXAMPLE 4 – Evidence Integration" in the Chemical-specific Examples Demonstrating Implementation of NRC Recommendations document.

Currently, the IRIS Program is using existing guidelines that address these issues to inform assessments. In addition, the IRIS Program is taking a more systematic approach in analyzing the available human, animal, and mechanistic data is being used in IRIS assessments. In conducting this analysis and developing the synthesis, the IRIS Program evaluates the data for the:

- strength of the relationship between the exposure and response and the presence of a dose-response relationship;
- specificity of the response to chemical exposure and whether the exposure precedes the effect;
- consistency of the association between the chemical exposure and response; and
- biological plausibility of the response or effect and its relevance to humans.

The IRIS Program uses this weight of evidence approach to identify the potential hazards associated with chemical exposure.

The IRIS Program recognizes the benefit of adopting a formal weight-of-evidence framework that includes standardized classification of causality. In addition to the NRC task, in which the panel will review current methods for evidence-based reviews and recommend approaches for weighing scientific evidence for chemical hazard and dose-response assessments, the IRIS Program is planning to convene a workshop to discuss approaches to evidence integration. As part of this workshop, the various approaches that are currently in use will be acknowledged and compared for their strengths and limitations. The workshop will include scientists with expertise in the classification of chemicals for various health effects. The workshop will be open to the public, and the details will be publicly announced.

The "Integration of Evidence Evaluation" section in the draft Handbook for IRIS Assessment Development in Appendix F is currently under development.

Selection of Studies for Derivation of Toxicity Values

NRC Recommendations:

- The rationales for the selection of the studies that are advanced for consideration in calculating the RfCs and unit risks need to be expanded. All candidate RfCs should be evaluated together with the aid of graphic displays that incorporate selected information on attributes relevant to the database.
- Establish clear guidelines for study selection.
- Balance strengths and weaknesses.
- Weigh human vs. experimental evidence.
- Determine whether combining estimates among studies is warranted.

Implementation:

Implemented

- **Selection of Studies for Dose-Response Analysis**

The IRIS Program has improved the process for selecting studies for derivation of toxicity values as well as increasing the transparency about this process by providing an improved discussion and rationale. Building on the individual study quality evaluations (described under *Evidence Evaluation: Hazard Identification* in this report) that identify strengths and weaknesses of individual studies, for each health effect for which there is credible evidence of hazard, a group of studies are identified and evaluated as part of the hazard identification. In evaluating these studies for selecting a subset to be considered for the derivation of toxicity values, the basic criterion is whether the quantitative exposure and response data are available to compute a point of departure (POD). can be a no-observed-adverse-effect-level [NOAEL], lowest-observed-adverse-effect-level [LOAEL], or the benchmark dose/concentration lower confidence limit[BMDL/BMCL]).

Additional attributes (aspects of the study, data characteristics, and relevant considerations) pertinent to derivation of toxicity values are used as criteria to evaluate the subset of studies for dose-response analysis. Thus, the most relevant, informative studies are selected to move forward. The new document structure provides for transparent discussion of the studies identified for dose-response analysis.

For more detailed information, see "Selection of Studies for Derivation of Toxicity Values" in the Dose-Response Analysis section in the draft Handbook for IRIS Assessment Development in Appendix F.

See also Section 6 ("Selecting studies for dose-response analysis") in the Preamble to IRIS Toxicological Reviews in Appendix B.

Appendix B – Preamble to IRIS Toxicological Reviews

1. Scope of the IRIS Program

Soon fter EPA as established in 970, it was at the orefront of veloping isk assessment as science nd applying decisions rotect human health and the environment. The lean Air ct, for example, ndates that EPA provide "an ample rgin afety to protect health"; the Safe Drinking Water Act, that "no adverse effects e health persons may reasonably be anticipated o occur, allowing adequate margin afety." Accordingly, EPA uses formation e dverse effects chemicals exposure levels below which these effects are not anticipated to occur.

IRIS assessments ritically eview the publicly available tudies to dentify adverse health effects from long-term exposure to chemicals and to characterize exposure-response relationships. In terms et forth by the ional Research Council (NRC, 1983), IS assessments cover the hazard identification nd dose-response assessment eps of isk ssessment, not he exposure ssessment or isk characterization steps at are onducted by EPA's program and regional ffices and by er ederal, state, and local health gencies at evaluate pecific populations nd exposure cenarios. IRIS assessments are distinct from and do not address political, economic, and technical onsiderations that influence the design and selection of risk management alternatives.

An IRIS assessment may cover a single chemical, a roup tructurally logically elated chemicals, omplex mixture. eptions re chemicals currently used exclusively as pesticides, ionizing and non-ionizing adiation, and criteria ir pollutants isted under ection 108 of e lean ir ct (carbon noxide, lead, nitrogen oxides, ozone, particulate matter, and sulfur oxides).

Periodically, the RIS rogram asks r PA programs nd egions, other federal agencies, state health agencies, and the general public to nominate chemicals and mixtures for future assessment r eassessment. These agents may be nd in ir, water, soil, or sediment. Selection is ram and egional fice iorities and on vailability dequate information o evaluate the potential for dverse effects. The IRIS Program may assess other agents as an urgent public health need arises. IRIS also reassesses published.

2. Process for developing and peer-reviewing IRIS assessments

The process for developing IRIS assessments (revised in y 009) volves critical nalysis the pertinent studies, portunities or ublic input, and multiple levels of scientific eview. EPA vises draft assessments after each eview, and ternal drafts d omments ecome part of e ublic cord (U.S. PA, 2009).

Step 1. Development of a draft Toxicological Review (generally out -1/2 ths duration). he raft assessment onsiders all pertinent blicly ailable studies and applies onsistent criteria to evaluate study quality, identify ealth ffects, identify mechanistic events nd pathways, tegrate the evidence f ausation for each effect, nd derive ity values. A public dialogue meeting prior to the integration f evidence and derivation of toxicity alues romotes public discussion of the literature search, evidence, and key sues.

Step 2. Internal review by scientists in EPA programs and regions (2 months). The draft assessment is revised to address comments om ithin EPA.

Step 3. Interagency science consultation with other federal agencies and the Executive Offices of the President (1-1/2 onths). The draft ssessment is evised o address the interagency comments. The science consultation draft, teragency nts, and EPA's response to major omments become part of the public record.

Step 4. Public review and comment, followed by external peer review (3-1/2 months more, epending on e review rocess). EPA releases the draft ssessment for public review nd omment. Another blic dialogue meeting provides n portunity discuss the assessment rior o peer view. EPA addresses the public omments and releases raft or external peer review. The peer eviewers assess hether he evidence has been assembled nd evaluated cording to guidelines and whether e conclusions are justified by he evidence. The peer review eeting is open e public and includes time or ral ublic comments. The peer review draft, peer eview eport, and written public omments become part of the public cord.

Step 5. Revision of draft Toxicological Review and development of draft IRIS summary (2 months). The aft assessment is revised to reflect the peer eview comments, public comments, nd newly ublished studies that are critical e conclusions of the assessment. The disposition of eer review comments nd public ments ecomes part of the ublic record.

Step 6. Final EPA review and interagency science discussion with other federal agencies and the Executive Offices of the President (1-1/2 months). he draft assessment nd summary are revised to address A nd eragency comments. The science cussion draft, ritten agency comments, and EPA's esponse to major comments become art e ublic ecord.

Step 7. Completion and posting (1 month). The Toxicological Review d RIS mmary are posted on e IS web ite (http://www.epa.gov/iris/).

The remainder of this Preamble addresses step 1, the evelopment of ft Toxicological Review. IRIS assessments low tandard practices f evidence evaluation n n which are discussed n PA guidelines (U.S. EPA, 1986a, 986b, 1991, 1996, 1998, 2000, 005a, 2005b) nd ther methods (U.S. EPA, 1994, 2002, 2006a, 2006b, 2011, 2012a, 2012b). A practical draft *Handbook* is available for use by IRIS assessment eams (U.S. EPA, 2013). Transparent application f scientific dgment is of paramount importance. To rovide harmonized approach cross IRIS assessments, this Preamble summarizes concepts hese guidelines and emphasizes rinciples of eneral applicability.

3. Identifying and selecting pertinent studies

3.1 Identifying studies

Before eginning n assessment, A onducts a comprehensive earch the primary cientific literature. The iterature search follows standard practices nd ncludes he PubMed and ToxNet databases f the National Library of edicine, Web of cience, and other atabases ted n EPA's HERO system Health and nvironmental Research line, http://hero.epa.gov/). rches for nformation on mechanisms toxicity e inherently specialized and may include studies on ther gents that act through related mechanisms.

Each assessment pecifies he search strategies, keywords, and ut-off dates of iterature searches. EPA posts e esults e iterature search n e IRIS web ite and requests information from e ublic on additional studies and ngoing search.

EPA iders studies received through IRIS Submission Desk nd studies typically unpublished) bmitted e the oxic Substances Control Act or e Federal Insecticide, Fungicide, nd Rodenticide Act. aterial submitted onfidential Business mation is sidered only udes health and safety data that an be publicly eleased. If a study that may be critical to the conclusions of e assessment has not been peer-reviewed, EPA will have peer-reviewed.

EPA also examines the toxicokinetics of the agent to identify other chemicals (for example, major metabolites of the agent) lude e assessment q information is available, in rder to more ully lain e xicity of e agent and to suggest dose etrics for ubsequent modeling.

In assessments of chemical mixtures, mixture studies e preferred for eir ability eflect interactions mong omponents. The erature search seeks, in decreasing order eference (U.S. EPA, 1986a, 2000):

- Studies of the being assessed.
- Studies ufficiently similar mixture. In evaluating imilarity, the ssessment considers the alteration of mixtures in e environment hrough partitioning nd transformation.
- Studies of dividual hemical components of the mixture, if there re ot adequate studies of fficiently ar mixtures.

3.2 Selecting pertinent epidemiologic studies

Study esign the ey onsideration for selecting ertinent epidemiologic tudies from the results of the literature search.

- Cohort studies, case-control studies, some opulation-based surveys (for example, NHANES) provide the strongest epidemiologic idence, pecially when they collect information bout individual exposures effects.
- Ecological tudies (geographic correlation studies) relate exposures f by geographic area. They an rovide trong evidence if there are large exposure contrasts between geographic as, relatively ittle exposure ariation within study areas, and population migration is limited.
- Case ports igh or cidental exposure lack finition the ulation t risk nd the expected number of ses. -hey can provide information bout rare effect or about the relevance of analogous results in animals.

The assessment briefly reviews ological studies and case reports ut eports tails only if ey suggest effects not identified by other studies.

3.3 Selecting pertinent experimental studies

Exposure route is a key design consideration for selecting ertinent experimental animal studies or uman inical studies.

- Studies f al, nhalation, ermal exposure volve passage rough n absorption barrier and are considered most pertinent to n v onmental exposure.
- Injection lantation tudies are often considered less pertinent but may provide valuable okinetic echanistic information. They lso may be seful for identifying effects n nimals eposition or absorption roblematic (for example, for particles d fibers).

Exposure duration is also a key esign consideration for selecting ertinent experimental animal studies.

- Studies of fects from chronic exposure are most pertinent to ifetime uman exposure.
- Studies fects from less-than-chronic exposure are pertinent but less preferred for identifying effects rom time uman exposure. uch tudies may be indicative of effects -than-lifetime human exposure.

Short-duration tudies involving imals or humans may provide okinetic or mechanistic information.

For developmental toxicity and reproductive toxicity, irreversible effects may result from a brief exposure during ritical period of development. Accordingly, specialized udy designs re used or hese effects U.S. EPA, 991, 1996, 1998, 2006b).

4. Evaluating the quality of individual studies

After the bsets of ertinent epidemiologic n experimental tudies ave een elected rom the literature ar hes, the assessment valuates the quality each ndividual study. This evaluation considers the esign, methods, conduct, nd documentation of each study, ut not whether the results are positive, negative, or null. The objective is to identify the stronger, more informative studies based on a uniform evaluation f quality haracteristics across studies f similar esign.

4.1 Evaluating the quality of epidemiologic studies

The assessment evaluates ign and methodological spects at can crease or decrease the weight given to ach epidemiologic study n he overall evaluation (U.S. EPA, 1991, 1994, 996, 1998, 2005a):

- Documentation of study design, ethods, population haracteristics, nd results.
- Definition and selection of he tudy group and comparison group.
- Ascertainment of exposure to the chemical or ixture.
- Ascertainment of disease or health ffect.
- Duration xposure nd follow-up nd adequacy for assessing the occurrence of effects.
- Characterization of exposure during critical periods.
- Sample ize and statistical power to detect anticipated effects.
- Participation ates and potential or election bias as a result of the chieved participation rates.
- Measurement error (can lead to misclassification exposure, health outcomes, and other factors) and other types of information bias.
- Potential confounding nd other sources of bias addressed in e tudy design n analysis sults. The basis consideration founding expectation at the confounder is related to both exposure nd outcome and is sufficiently prevalent to result in bias.

For developmental toxicity, reproductive toxicity, neurotoxicity, and cancer there is further guidance on the nuances evaluating epidemiologic tudies of ese effects U.S. EPA, 1991, 1996, 1998, 005a).

4.2 Evaluating the quality of experimental studies

The assessment evaluates design and methodological spects at can crease or decrease the weight iven to ch experimental animal study, in-vitro tudy, or linical study (U.S. A, 1991, 994, 1996, 998, 2005a). Research involving uman ubjects considered only if conducted according to ethical principles.

- Documentation of tudy design, nimals study population, methods, basic ta, and results.
- Nature e ssay intended urpose.
- Characterization of the nature and extent of impurities nd contaminants e administered chemical or
- Characterization of e nd ing regimen (including e t exposure) and their adequacy licit effects, including latent effects.
- Sample sizes nd tistical power detect dose-related differences r rends.
- Ascertainment of urvival, vital signs, disease or effects, d use of eath.
- Control other ariables that could influence the occurrence of effects.

The ssessment uses statistical sts evaluate whether he observations may e due to hance. The standard for etermining statistical significance of esponse is a trend test or comparison tcomes n the exposed groups against those of concurrent controls. In some situations, examination of historical control ta from the same laboratory within a few ears of the tudy may mprove e nalysis. For n uncommon effect that is ot statistically significant compared with oncurrent controls, historical controls y show at the ffect unlikely to be due to chance. For a response at appears ignificant against urrent ontrol response at is nusual, istorical ontrols y offer ifferent interpretation (U.S. EPA, 2005a).

For evelopmental toxicity, reproductive , neurotoxicity, nd cancer there is further guidance on he nuances of evaluating experimental studies f these effects U.S. EPA, 1991, 1996, 1998, 2005a). In multi-generation studies, agents that produce developmental effects t doses that are not toxic e aternal animal re pecial concern. Effects at occur at doses ssociated with ild maternal toxicity are not assumed to result only from maternal toxicity. Moreover, maternal effects may reversible, hile ffects he fspring y be permanent U.S. EPA, 991, 1998).

4.3 Reporting study results

The assessment uses idence tables to present the sign nd key esults ertinent studies. There may be separate tables or each site of toxicity or type of tudy.

If rge mber tudies observe the me effect, e ssessment considers e tudy quality characteristics ection entify the strongest studies or pes tudy. The tables present details from these studies, and the assessment xplains the reasons r not reporting etails ther tudies r roups studies at not dd new information. Supplemental information provides eferences to all tudies onsidered, cluding those ot summarized in e bles.

The assessment discusses strengths and limitations that affect the interpretation ch study. If the interpretation of a study e assessment differs rom that of e dy uthors, the ssessment discusses the basis for the difference.

As a check on the selection and evaluation of pertinent udies, EPA asks peer reviewers to identify tudies at were not adequately considered.

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5. Evaluating the overall evidence of each effect

5.1 Concepts of causal inference

For each ealth ect, the sessment evaluates the evidence as whole to determine whether t is reasonable to infer ausal association between exposure to the agent and the occurrence of the ect. his ference ased on information ertinent human tudies, animal studies, and mechanistic studies of adequate quality. Positive, negative, and null results are given weight according to study quality.

Causal ference involves scientific dgment, and he onsiderations e nuanced d mplex. Several health gencies ave eveloped frameworks or ausal inference, mong them the U.S. rgeon General (DHEW, 1964; DHHS, 2004), the nternational Agency for Research n Cancer 2006), nstitute of edicine 2008), and he .S. Environmental Protection Agency (2005a, 2010). Although eveloped or different purposes, the frameworks re imilar in nature and provide n tablished tructure d language for ausal inference. Each onsiders aspects of n ssociation at suggest ausation, discussed by Hill (1965) and elaborated by Rothman nd Greenland (1998) (U.S. EPA, 1994, 2002, 2005a).

Strength of association: The finding of relative isk with arrow onfidence intervals trongly uggests hat an association e to chance, bias, or other factors. Modest relative s may eflect a small range of exposures, agent of w potency, an ncrease in n ffect that is common, exposure misclassification, or other sources f bias.

Consistency of association: An inference f causation trengthened if elevated risks are bserved n independent tudies of different populations nd exposure scenarios. Reproducibility of indings constitutes one of the trongest arguments for ausation. Discordant results sometimes reflect differences tudy design, exposure, or onfounding actors.

Specificity of association: As riginally intended, this refers to one ause ociated with ne effect. urrent standing at many gents ause ltiple effects d ny effects have multiple causes make this ss informative aspect ausation, ess e effect is rare or nlikely ave ltiple causes.

Temporal relationship: A ausal interpretation requires at e precede development of the effect.

Biologic gradient (exposure-response relationship): Exposure-response relationships strongly ggest causation. A monotonic crease ot the ly attern consistent with usation. The presence of an exposure-response radient also weighs against bias d confounding s ource of an ssociation.

Biologic plausibility: An inference of causation is trengthened by emonstrating plausible biologic mechanisms, vailable. Plausibility may reflect subjective prior beliefs ere insufficient understanding of e biologic process involved.

Coherence: An nference causation strengthened by upportive results rom animal xperiments, toxicokinetic tudies, and hort-term tests. Coherence may also e found er ines evidence, such s changing disease patterns in he population.

"Natural experiments": A change in exposure that rings about a change in disease frequency provides strong evidence, as tests e ypothesis of ausation. An example would be ntervention reduce exposure in e workplace nvironment that is followed y eduction of an adverse effect.

Analogy: Information uctural analogues r on chemicals that induce imilar mechanistic events can provide insight into causation.

These onsiderations are onsistent with guidelines for ystematic eviews at evaluate the quality nd eight of evidence. Confidence is increased if the magnitude ge, there is vidence n exposure-response relationship, or f ssociation was served and the ses would tend o decrease the magnitude the reported effect. Confidence is decreased r study imitations, inconsistency of esults, indirectness f evidence, imprecision, or reporting ias Guyatt et al., 2008a,b).

5.2 Evaluating evidence in humans

For each effect, the ssessment evaluates the evidence rom e pidemiologic dies as whole. to determine whether a credible sociation as been bserved d, if so, whether at association sistent with causation. In doing this, the assessment explores alternative explanations (such as chance, bias, and confounding) and draws a conclusion about whether these lternatives can satisfactorily explain ny bserved association.

To make ear ow much the epidemiologic evidence contributes to e overall weight of the evidence, the assessment may elect a tandard descriptor haracterize the epidemiologic evidence ssociation between exposure to the agent d occurrence f ealth ffect.

Sufficient epidemiologic evidence of an association consistent with causation: The evidence establishes ausal ssociation or which lternative explanations such as chance, bias, and onfounding an be ruled out with reasonable onfidence.

Suggestive epidemiologic evidence of an association consistent with causation: The evidence suggests ausal ssociation but chance, bias, or confounding annot e ruled out as xplaining the ssociation.

Inadequate epidemiologic evidence to infer a causal association: The available studies o not permit a clusion egarding e presence or absence of n ssociation.

Epidemiologic evidence consistent with no causal association: Several adequate studies covering e full ge f human exposures and considering usceptible populations, and for which alternative explanations ch bias and confounding can be ruled out, are mutually consistent in not finding an association.

5.3 Evaluating evidence in animals

For each effect, the assessment valuates the evidence rom e nimal experiments s whole to determine the extent to h indicate a potential for effects n mans. onsistent results across various species and strains increase confidence at similar results would occur in humans. Several concepts discussed by Hill (1965) are rtinent to the weight of experimental results: consistency of response, dose-response relationships, trength response, biologic plausibility, and coherence (U.S. EPA, 1994, 2002, 2005a).

In eighing vidence from multiple experiments, U.S. EPA 2005a) distinguishes

Conflicting evidence (that is, mixed positive and negative results the ame sex and strain using imilar tudy protocol)
Differing results (that is, positive results nd negative results are in ifferent exes or strains or use different study protocols).

Negative or null results do not invalidate positive results in a different experimental system. PA regards d bservations d looks explain fering results sing echanistic information (for example, physiologic metabolic differences across st systems) or methodological differences (for example, relative sensitivity e ests, fferences in e evels, insufficient sample ize, or dosing r data

It is l established that there re critical periods or ome evelopmental and reproductive fects. ccordingly, the assessment determines whether ritical periods have been adequately nvestigated U.S. EPA, 1991, 1996, 1998, 2005a, 2005b, 2006b). Similarly, the assessment determines whether he atabase is adequate to evaluate other critical sites and effects.

In evaluating evidence of genetic toxicity:

- Demonstration gene tations, chromosome errations, or neuploidy in humans xperimental mammals (*in vivo*) provides e rongest evidence.
- This is followed by positive results in lower organisms or in cultured cells (*in vitro*) or other genetic events.
- Negative results arry less weight, partly because ey cannot exclude e ossibility of effects in other tissues IARC, 2006).

For germ-cell tagenicity, EPA as defined categories f evidence, ranging om itive results of human germ-cell mutagenicity negative results for ll effects of oncern (U.S. EPA, 1986b).

5.4 Evaluating mechanistic data to identify adverse outcome pathways and modes of action

Mechanistic ata can be seful in answering several uestions.

- The iologic plausibility of a causal interpretation tudies.
- The generalizability of animal studies to humans.
- The usceptibility of particular populations or ifestages.

The focus e nalysis is o describe, if possible, *adverse outcome pathways* that lead to a health ffect. n dverse outcome pathway encompasses:

- *Toxicokinetic processes* of , distribution, metabolism, nd elimination that lead to e formation of an active t and its presence at the site of initial biologic interaction.
- *Toxicodynamic processes* that ad o ealth effect at this or another ite (also known s a *mode of action*).

For each effect, the assessment discusses the available formation on its *modes of action* and associated *key events* (*key events* being empirically bserv le, necessary r steps or biologic markers such teps; *mode of action* being a ries f key events olving interaction with ells, operational and anatomic changes, and resulting in disease). Pertinent information y also come rom studies of metabolites or ompounds at are structurally similar at act through mechanisms. Information on e of action is not required for a conclusion that the agent is causally related to an effect (U.S. EPA, 2005a).

The assessment addresses several questions about each ypothesized mode of action (U.S. EPA, 005a).

(1) Is the hypothesized mode of action sufficiently supported in test animals? Strong upport r a ey event being necessary to a e of ction an ome from experimental challenge to the hypothesized mode of action, in which studies that

Evaluation and Display of Individual Studies

STUDY QUALITY EVALUATION

Study Quality Evaluation: Overview

- Be inclusive: t etter o de a study d aluate effects of potential limitations an o exclude a study and iminate any nformation the study could have provided
- Evaluate studies BEFORE developing evidence tables
- Series of ocused uestions; pplied stematically to all primary data studies identified elevant he screening steps
- Evaluation is ndpoint-specific; a given tudy aluating everal endpoints may have ifferent strengths nd imitations ith spect to ach endpoint

Study "quality," as defined erein, s a road erm encompassing terpretations regarding a variety of methodological features ., study esign, posure measurement etails, study execution, data analysis nd presentation). The purpose of this step n he systematic eview process is not to eliminate udies, ut ather o evaluate studies with espect o otential methodological considerations hat ould affect he interpretation f or nfidence in he results. For larger atabases, n articular, this aluation can rovide a transparent means to onvey our assessment of a study's methodological strengths and limitations, and thus your ability o ely n the results. e esults of his systematic evaluation may also inform decisions about which studies to ove forward or dose-response modeling vation

The systematic evaluation escribed in his step ould e nducted at an rly age assessment development, .e. fter dentifying the relevant ources rimary data but efore developing evidence tables and characterizing hazards associated ith posure to hemical. All studies dentified elevant from the literature screening process hould e evaluated. Even a deficiency n ect of the udy is obvious, it he valuation of all of the component questions o hat ull record of the evaluation e maintained.

Examination f specific methodological features of each study can be ccomplished by applying ries of ocused starting point for generating these ssessment and endpoint ecific questions would be to consider the examples provided in Tables F-6 and F-7 for observational epidemiology and imal toxicology udies, espectively. Documentation important ethodological ures f a study may e an erative process, requiring odification an initial set of questions, as specific features of the chemical, endpoint(s), or study design(s) are discovered. It is essential that hese focused uestions be pplied uniformly to all studies evaluated. This will llow or mparison f the considered studies that is both stematic in design d ependent of the study results. Ideally, wo eviewers would ndependently dentify the relevant methodological details, and then compare their results and interpretations and resolve any differences.

For udies that amine more than ne endpoint or utcome, the evaluation process should be endpoint-specific, s the utility udy may ary for he ferent endpoints.

The methods section he paper ill generally rovide the majority of information needed for this aluation except, of course, for considerations elating to the level of detail of the reported esults). In some cases, however, study details may be presented elsewhere in the manuscript or report, such s the troduction r iscussion sections. dentification f ome study details may equire additional investigation, for example, by consulting ther publications describing the study or udies on he liability of an ay, or by contacting he udy uthors. n general, study uality evaluation hould be independent of considerations egarding he direction or magnitude of he ' esults.

It s useful to check the citation in one of the primary databases (e.g., PubMed) to see if there is any linked material, such ratum, supplementary pendix material, letter to the editor (and authors' reply) regarding the citation, or ompanion udy is kind of preliminary work can prevent significant heartburn d eadaches in subsequent steps.

It s seful to record he pertinent ethodological features sy o form (e.g., a tabular format) so at these study details can be easily eviewed. ecause observational epidemiology and animal toxicology studies have fundamental differences, the documentation and evaluation of these studies will differ.

There may e situations, most mmonly hen tensive literature databases ist r a given chemical and effect, in hich n dividual study or sets of udies can be xcluded from further consideration. For example, acute animal toxicology studies ay cluded hen abundant bchronic and ronic exposure studies examining imilar dpoints are available.

The ollowing discussion tudy uality luation ocused valuation observational epidemiology, animal toxicology, d human ontrolled posure studies. This approach could also be dapted r the evaluation of in vitro studies d other ypes f studies relevant to mechanisms f action.

Study Quality Evaluation: Logistics

- Methods section of the study should rovide most of he nf mation you need; study quality evaluation should be independent of considerations regarding the direction r gnitude f the study's results
- Look r rata, supplemental files, and ther aterial linked to the primary data citation or additional information bout the study
- Published correspondence (e.g., ters o the editor, editorials) may rovide additional ackground information mportant ethodological features.
- Ideally, use two *independent* reviewers, with procedures for disagreements to be reviewed d esolved

Evaluation of Observational Epidemiology Studies

The rocess of study evaluation is akin o tective ork. You need to investigate specific study ures hat ectly t he interpretation of the experimental results, including:

- exposure measures (reliability, validity, probability and el of exposure in ifferent situations or settings)

- outcome measures reliability, dity, prevalence in ifferent populations, disease course, relation een urvival and cess o ealth care or ther socioeconomic factors)
- confounders (strong risk actors or he come that are also known to be strongly associated with he exposure within he study)

These investigations may equire mini-reviews" and onsultation with experts in ifferent fields. Without this background understanding, you may t e able to curately aluate the studies.

Exposure assessment is pecially important in the environmental or occupational arena. The bility o correctly assify xposed" and "unexposed", te quantitative measures of exposure, and the range of exposure encompassed in the study is ey ifference between observational epidemiology and andomized clinical trials n which "exposure" (e.g., "intention o treat" or type of treatment) may be less subject to measurement error and the exposure contrast s less variable between studies.

As noted ove, an inclusive approach is enerally recommended: that is, it etter o include a study is systematic evaluation and xamine the impact of tential limitations, ather than exclude a study and thus lose any information it ould have provided. or demiology studies, to the extent possible, you want to assess ot st e "risk f bias," ut also he likelihood, direction, and magnitude of bias.

The study haracteristics that form the evaluation of observational epidemiology studies are summarized in able F-6. The first feature, the type of study esign, provides amework for the subsequent aluation; that s, the specific uestions and issues ill vary epending on he type of study. he other ures compass spects f the study opulations, exposure measures, outcome (effect) measures, and the analysis d resentation of results. Although eneral your evaluation he sults is eeded, for ample within the context of the evaluation of confounding, since confounding depends n he strength of various relationships (i.e., between the exposure and the potential confounder d between he potential confounder and he outcome).

A structured orm may be useful for ecording he key ures ed aluate a study. An example form is shown in Figure F-3; details of such a orm will eed o e modified ased n the specifics of the chemical, exposure scenarios, and effect measures nder study.

Study Quality Evaluation: Observational Epidemiology Studies

- As oted n he overview, the evaluation process is inclusive in ature, is conducted BEFORE developing idence tables, uses eries of systematically applied, focused questions, and is end-point specific
- Do our etective work head f time: vestigate exposure measures, effect measures, and confounders for he chemical-effect der review
- To the extent possible, assess likelihood, direction, and magnitude of bias

Table F-6. General Considerations for Evaluation of Features of Epidemiology Studies

Feature	Example Questions or Details	Useful Information
Study design	Major types, based on approach to sample selection: cohort, case-control, nested case-control, population-based survey (e.g., NHANES), times series, case crossover	Study methods
Study population; target population; setting	Where and when was the study conducted? What is the source(s) of exposure (environmental media, consumer products, occupational, an industrial accident, or other)? What was the recruitment process? How was eligibility determined? Does the study provide information on potential vulnerable or susceptible groups? Address: Potential generalizability of study results, potential for selection bias, potential to address effect modification	Geographic area, site (occupational, etc.), time period. Age and sex distribution, other details as needed (may include race/ethnicity, socioeconomic status); recruitment process; exclusion and inclusion criteria
Participation rate; follow-up	Did rates vary by exposure (or disease) status? Were there differences between individuals who did and did not participate, or who were or were not lost to follow-up? Is it known (or possible) that participation (or loss) is related **both** to exposure **and** disease status? Is there evidence of "healthy worker" or "healthy worker survivor" effect? Are differences likely to impact the observed associations (and if so, how)? Address: Potential for selection bias	Total eligible; participation at each stage and for final analysis group; loss to follow-up, denominators used to make these calculations; length of follow-up
Comparability (exposed and non-exposed; cases and controls)	How were potential differences between groups addressed in the study design (e.g. randomization, restriction, matching) and/or analysis (e.g. stratification, multivariate methods)? How were variables associated with exposure and with outcome, or which alter the association between exposure and outcome, addressed in the study? Address: potential for confounding and effect modification	"Table 1" type participant characteristic data, by group; approach to consideration of potential confounding (if applicable); strength of associations between exposure and potential confounders and between potential confounders and outcome
Exposure measures (procedure, range)	Are exposure estimates qualitative, semi-quantitative or quantitative? How well does the exposure protocol correctly classify or rank participants with respect to exposure? What is the likelihood of systematic (differential) error? What is the likelihood of random (non-differential) error? Does the protocol adequately characterize exposure during the relevant time window? What exposure range is spanned in this study? Address: potential for exposure misclassification (either non-differential or differential)	Describe, i.e., type of biomarker(s), occupational history, lifetime consumption, evidence from validation studies, variability within and between exposure groups
Outcome measures	What is source of outcome (effect) measure? How well do the outcome(s) measures correctly classify participants with respect to the outcome? What is the likelihood of systematic (differential) error? What is the likelihood of random (non-differential) error? Address: potential for outcome misclassification (either non-differential or differential)	Describe (i.e., source, how measured/classified, incident versus prevalent disease), evidence from validation studies
Data Presentation and Statistical Analysis	Is the analysis appropriate for the data and the study question? Are aspects of the data (i.e., non-normal distributions, correlation structure) adequately accounted for? Is the rationale for inclusion of variables in a model clear and logical? Are results presented with adequate detail? Is the study population of adequate size and composition to detect a true association (of a relevant effect size) between exposure and outcome? Were stratified analyses (effect modified) motivated by a specific hypothesis? Address: ability to interpret and level of confidence in results	How groups are compared (may include t-tests, ANOVA, regression models, etc.); what results are presented in text, tables, and figures; n exposed cases (case-control studies) or N cases among exposed (cohort studies)

APPENDIX C – 22

From: SandP8
To: Katherine Walker; Kane, Agnes; Diana-M Wong/DC/USEPA/US@EPA
Subject: Re: Language To Clarify Your View
Date: 10/01/2012 05:53 PM

Diane, Agnes:

I agree with Katy completely.

She said she'd reduce her commentary to a concrete suggestion about the text. I would concur (if that still matters) with any language suggestion she's comfortable with.

Scott

On Mon, Oct 1, 2012 at 5:27 PM, Katherine Walker <KWalker@healtheffects.org> wrote:
Yes. Will give it a whirl later. I was in a meeting when I wrote that. Will cut it down and resend. You will need to respond and concur or revise.

Sent from my iPhone

On Oct 1, 2012, at 5:04 PM, [redacted]

As you know, I agree with you completely. Do you wanna make a specific suggestion about wording? Just omit mentioning the one point, or something broader?

Scott

On Mon, Oct 1, 2012 at 12:04 PM, Katherine Walker <<mailto:KWalker@healtheffects.org>KWalker@healtheffects.org<mailto:KWalker@healtheffects.org>> wrote:
I think the addition of 'may be' helps but the 'However..." that follows refers to just one of several recommendations we made that are targeted at trying to characterize the limitations or uncertainties that that may result from that choice, including the choice of models used to analyze a limited data set. I'm not sure I would want to single out the mortality v incidence issue alone.

I think we want to make the broader point - that they have made a number of data selection and analysis choices tha may be reasonable but that it is important to convey to risk analysts and to policy makers a broader perspective. That is the basis for a number of recommendation for sensitivity analyses that we made.

The NAS and others have made recommendations for 20 years or more that uncertainties need to be more clearly and quantitatively, if possible, portrayed. That was the spirit of our recommendations recognizing that it wasn't possible to do a full uncertainty analysis.

I think this is very important.

Katy

Sent from my iPhone

On Oct 1, 2012, at 11:37 AM, "Diana-M Wong" <<mailto:Wong.Diana-M@epamail.epa.gov>Wong.Diana-M@epamail.epa.gov<mailto:Wong.Diana-M@epamail.epa.gov><mailto:<mailto:Wong.Diana-M@epamail.epa.gov>Wong.Diana-M@epamail.epa.gov<mailto:Wong.Diana-M@epamail.epa.gov>>> wrote:

Scott,

Thank you for your response.

Based on your suggestion, the statement in the cover letter is revised to:

" The SAB supports the selection of the Libby worker cohort for the derivation of the inhalation unit risk (IUR) and agrees that the use of the subcohort post-1959 for quantification may be reasonable due to the lack of exposure information for many of the workers in earlier years. The SAB finds it appropriate to use lung cancer and mesothelioma as endpoints for the derivation of the IUR. However, the SAB recommends a more detailed discussion and justification of how the use of mortality data rather than incidence data may have resulted in an undercount of cases of lung cancer and mesothelioma."

To be consistent, I will make similar change to line 27, page 3 of the Executive Summary of the August 30 draft. Please let me know if this change satisfies your concern.

Sincerely,

Diana Wong, Ph. D., DABT
Toxicologist and Designated Federal Officer
USEPA
Science Advisory Board Staff Office
MC: 1400R
1200 Pennsylvania Ave, N.W.
Washington, DC 20460

Phone:(202) 564-2049<tel:%28202%29%20564-2049>

<graycol.gif>SandP8 ---10/01/2012 10:59:09 AM---Diana, Agnes: Thanks for your suggested edit. I think it would be great. I apologize

From: [redacted]
To: Diana-M Wong/DC/USEPA/US@EPA
Cc: "<mailto:scott@ramas.com>scott@ramas.com<mailto:scott@ramas.com><mailto:<mailto:scott@ramas.com>scott@ramas.com<mailto:scott@ramas.com>>"
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<<mailto:KWalker@healtheffects.org>KWalker@healtheffects.org<mailto:KWalker@healtheffects.org><mailto:<mailto:KWalker@healtheffects.org>KWalker@healtheffects.org<mailto:KWalker@healtheffects.org>>>, "Kane, Agnes"
<<mailto:agnes_kane@brown.edu>agnes_kane@brown.edu<mailto:agnes_kane@brown.edu><mailto:<mailto:agnes_kane@brown.edu>agnes_kane@brown.edu<mailto:agnes_kane@brown.edu>>>
Date: 10/01/2012 10:59 AM
Subject: Re: Language To Clarify Your View

Diana, Agnes:

Thanks for your suggested edit. I think it would be great. I apologize for forcing you to read my mind about this. I suggested a much more modest change in the explanation promised to Agnes that I wrote after speaking to Katherine Walker last week:

I do not agree that the use of the subcohort post-1959 for quantification is "reasonable" due to the lack of exposure information for many of the workers in earlier years. It *may* be reasonable, but I think it improper to say that it *is* reasonable. At best, it is a modeling choice that some but certainly not all people would make. In my estimation, the Agency has not sufficiently explored the question of whether or not the lack, or rather paucity, of exposure data from earlier years invalidates or inhibits inferences. Those statistical questions have not really been asked. Thus, I cannot "support the selection of the Libby worker cohort" as stated in the bullet's main clause. I have no problem with the rest of the text of the bullet. As a way forward, it might suffice to simply change "is" to "may be" in the third verb of the first sentence. I understand that the explanatory text on this matter persists in the body of the submission.

Sorry if this has been much ado about nothing, but the tone of the bullet seemed too much of a whitewash to accept as a reflection of what we had discussed in our meetings.

Thanks for your patience with me. It's been rather difficult for me personally these last few weeks. I hope that I will soon be out of the woods, to use a corny expression.

Best regards,
Scott

On Thu, Sep 27, 2012 at 5:16 PM, Diana-M Wong <<mailto:Wong.Diana-M@epamail.epa.gov>Wong.Diana-M@epamail.epa.gov<mailto:Wong.Diana-M@epamail.epa.gov><mailto:<mailto:Wong.Diana-M@epamail.epa.gov>Wong.Diana-M@epamail.epa.gov<mailto:Wong.Diana-M@epamail.epa.gov>>> wrote:

Scott,

My last communication to you on August 29 was to request for your suggested changes regarding the following paragraph in the cover letter:

" The SAB supports the selection of the Libby worker cohort for the derivation of the inhalation unit risk (IUR) and agrees that the use of the subcohort post-1959 for quantification is reasonabl due to the lack of exposure information for many of the workers in earlier years. The SAB finds it appropriate to use lung cancer and mesothelioma as endpoints for the derivation of the IUR. However, the SAB recommends a more detailed discussion and justification of how the use of mortality data rather than incidence data may have resulted in an undercount of cases of lung cancer and mesothelioma."

Since you did not respond, I noted in the Panel Roster of the August 30 draft that you did not concur this draft.

During the quality review teleconference on Tuesday (September 25) by SAB, the SAB Chartered Board questioned the basis of your non-concurrence. Dr. Kane indicated that she received an e-mail from you that you were not feeling well and therefore unable to respond to her. Accordingly, the SAB Chair directed that I need to incorporate your suggested change or provide an explanation for your non-conccurrence. Based on my understanding of your concern, I proposed the following revised statement.

" The SAB supports the selection of the Libby worker cohort for the derivation of the inhalation unit risk (IUR) and the use of the subcohort post-1959 for quantification due to the lack of exposure information for many of the workers in earlier years. However, the SAB recommends EPA utilize interval statistics to evaluate the potential impact of omitting the Libby workers hired before 1959 if deemed feasible. The SAB finds it appropriate to use lung cancer and mesothelioma as endpoints for the derivation of the IUR. However, the SAB recommends a more detailed discussion and justification of how the use of mortality data rather than incidence data may have resulted in an undercount of cases of lung cancer and mesothelioma."

I look forward to receiving your response. Thanks.

Sincerely,

Diana Wong, Ph. D., DABT
Toxicologist and Designated Federal Officer
USEPA
Science Advisory Board Staff Office
MC: 1400R
1200 Pennsylvania Ave, N.W.
Washington, DC 20460

Phone:(202) 564-2049<tel:%28202%29%20564-2049><tel:%28202%29%20564-2049>

Diana:

It is the first day of classes today, and am finding it difficult to be thorough in my review of the document you sent. I cannot always observe the deadlines that you set and inform me about.

I do not concur with this statement in the letter:

The SAB supports the selection of the Libby worker cohort for the derivation of the inhalation unit risk (IUR) and agrees that the use of the subcohort post-1959 for quantification is reasonable due to the lack of exposure information for many of the workers in earlier years.

I thought I was paying close attention, but did not notice until now that earlier language had been so watered down to be a complete capitulation to what I continue to believe is a flawed idea.

I don't think I'm merely being grumpy here. Perhaps someone can talk me down, but I'm a bit surprised and disappointed. Unfortunately, I am very busy this week. I may be able to revisit this on Wednesday afternoon.

Regards,
Scott

EXPANDED FROM PRIOR PAGE TO INCREASE LEGIBILITY:

From: [redacted]
To: Diana-N Wong/DC/USEPA/US@EPA
Cc: "<mailto:scott@ramas.com>scott@ramas.com<mailto:scott@ramas.com><mailto:<mailto:scott@ramas.com>scott@ramas.com<mailto:scott@ramas.com>>"
<<mailto:scott@ramas.com>scott@ramas.com<mailto:scott@ramas.com><mailto:<mailto:scott@ramas.com>scott@ramas.com<mailto:scott@ramas.com>>>, Katherine Walker
<<mailto:KWalker@healtheffects.org>KWalker@healtheffects.org<mailto:KWalker@healtheffects.org><mailto:<mailto:KWalker@healtheffects.org>KWalker@healtheffects.org<mailto:KWalker@healtheffects.org
>>>, "Kane, Agnes"
<<mailto:agnes_kane@brown.edu>agnes_kane@brown.edu<mailto:agnes_kane@brown.edu><mailto:<mailto:agnes_kane@brown.edu>agnes_kane@brown.edu<mailto:agnes_kane@brown.edu>>>
Date: 10/01/2012 10:59 AM
Subject: Re: Language To Clarify Your View

Diana, Agnes:

Thanks for your suggested edit. I think it would be great. I apologize for forcing you to read my mind about this. I suggested a much more modest change in the explanation promised to Agnes that I wrote after speaking to Katherine Walker last week:

I do not agree that the use of the subcohort post-1959 for quantification is "reasonable" due to the lack of exposure information for many of the workers in earlier years. It *may* be reasonable, but I think it improper to say that it *is* reasonable. At best, it is a modeling choice that some but certainly not all people would make. In my estimation, the Agency has not sufficiently explored the question of whether or not the lack, or rather paucity, of exposure data from earlier years invalidates or inhibits inferences. Those statistical questions have not really been asked. Thus, I cannot "support the selection of the Libby worker cohort" as stated in the bullet's main clause. I have no problem with the rest of the text of the bullet. As a way forward, it might suffice to simply change "is" to "may be" in the third verb of the first sentence. I understand that the explanatory text on this matter persists in the body of the submission.

Sorry if this has been much ado about nothing, but the tone of the bullet seemed too much of a whitewash to accept as a reflection of what we had discussed in our meetings.

Thanks for your patience with me. It's been rather difficult for me personally these last few weeks. I hope that I will soon be out of the woods, to use a corny expression.

Best regards,
Scott

APPENDIX C – 23

Laura E. Kerper, Ph.D.
Heather N. Lynch, MPH
Lawrence C. Mohr, M.D.*
Julie E. Goodman, Ph.D., DABT
*Medical University of South Carolina

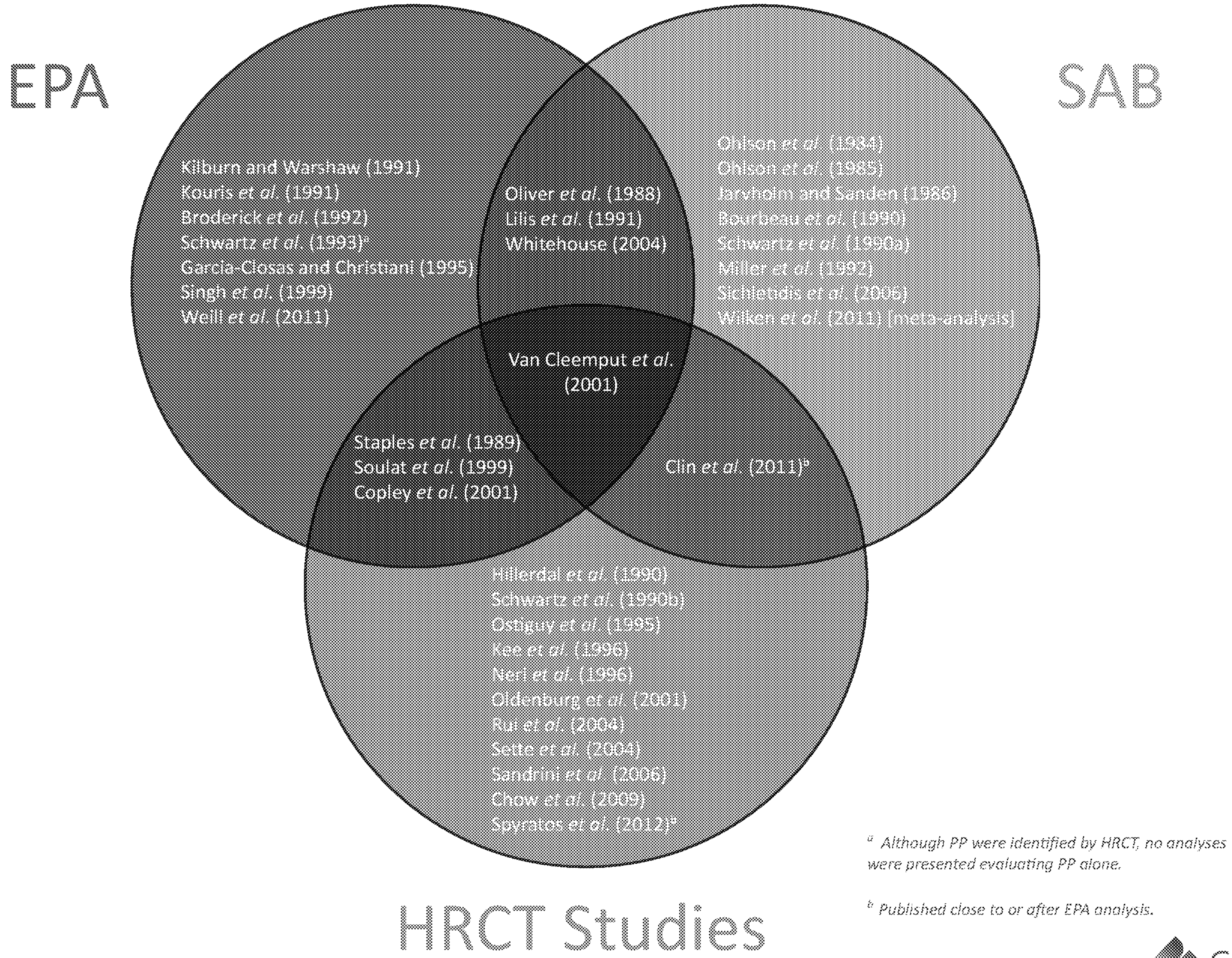
GRADIENT

SOT 2014 Annual Meeting
Abstract number 1811
Poster board 147

Do Asbestos-Induced Pleural Plaques Cause Lung Function Deficits?

While there is general agreement that pleural plaques are biomarkers of asbestos exposure, there is debate in the scientific community over whether pleural plaques cause lung function deficits. Many of the studies that addressed this issue were subject to certain limitations. In most studies, pleural plaques were diagnosed by radiography, which is less accurate than high resolution computed tomography (HRCT) and can lead to misdiagnoses. Some studies reported lung function changes in subjects that had lung abnormalities in addition to pleural plaques, so that the contribution of pleural plaques to deficits was unknown. To eliminate these sources of uncertainty, we conducted the first comprehensive analysis of the associations between pleural plaques and lung function based on epidemiology studies in which 1) pleural plaques were diagnosed by HRCT and 2) individuals were identified with pleural plaques and no other lung abnormalities. We identified and analyzed 16 relevant studies. We looked for patterns within and across studies and examined whether associations were reproducible. Only three of the 16 studies reported statistically significant associations between pleural plaques and some measure of lung function. Among these three studies, the lung function parameters were not consistent, suggesting that the associations were not likely causal. In addition, mean asbestos exposures in all three studies were higher in the subjects with pleural plaques than in the subjects without. This suggests that if the effects were not due to chance, the asbestos exposure itself, rather than pleural plaques, may have been responsible for observed lung function deficits. Taken as a whole, the direction of effect (*i.e.*, lung function deficit *vs.* improvement) varied among studies, indicating the absence of even subtle effects and that the lack of effect noted in the majority of studies was not a result of low statistical power. We conclude that there is no reliable association between the presence of pleural plaques in asbestos-exposed populations and lung function deficits.

Studies included in EPA, SAB, and HRCT study review of pleural plaques and lung function



GRADIENT

Pleural Plaques Diagnosed by High Resolution Computed Tomography (HRCT) and Lung Function in Asbestos-Exposed Populations.

This table summarizes associations between pleural plaques and lung function in studies in which 1) HRCT was used to diagnose or confirm the presence of pleural plaques, and 2) individuals with pleural plaques did not have other diagnosed lung abnormalities.

Study	No. of Participants	No. with Pleural Plaques Only	Cohort	Location	Asbestos Exposure Measure	Avg. Estimated Exposure	Measure of Lung Function	Result (Mean ± SD) Control	Result (Mean ± SD) Pleural Plaques	*p* value
Staples *et al.*, 1989	76	NR	Asbestos workers	US	Duration (mean years)	No PP: 14.5 With PP: 20.8	Air flow	NR	NR	>0.05
							Lung restriction	NR	NR	
							DL_{CO}	NR	NR	
Hillerdal *et al.*, 1990	23	13	Hospital pulmonary patients with occupational asbestos exposure	Sweden	Duration (mean years)	No PP: 0 With PP: 15-29	FEV_1, %	NR	98 ± 10	>0.05
							VC, %	NR	97 ± 11	>0.05
							FEV_1/VC	NR	98 ± 7	>0.05
							TLC, %	NR	96 ± 8	>0.05
							MVV, %	**NR**	**91 ± 11**	**<0.05**
							FEF_{50}, %	NR	95 ± 22	>0.05
							MEF/FEF_{50}, %	**NR**	**118 ± 27**	**<0.05**
Schwartz *et al.*, 1990	16	9	Sheet metal workers	US	Duration (years)	No PP: 33.3 ± 6.6 With PP: 30.3 ± 7.2	FEV_1, %	110.4 ± 9.1	100.1 ± 17.2	>0.05
							FVC, %	104.9 ± 6.7	96.0 ± 11.8	
							FEV_1/FVC	76.1 ± 6.4	75.1 ± 7.9	
							TLC, %	121.9 ± 12.5	116.7 ± 13.9	
							RV, %	120.7 ± 21.9	121.6 ± 42.5	
							DL_{CO}, %	111.6 ± 23.2	111.8 ± 16.3	
Ostiguy *et al.*, 1995	247	54	Copper refinery workers	Canada	Duration (years)	No PP: 25.7 ± 0.5 With PP: 26.8 ± 1.0	FEV_1, %	111	107	>0.05
							FVC, %	106	104	
							MMEF, %	114	106	
Kee *et al.*, 1996	106	44	Shipyard and construction workers	US	Duration (years)	26.5 ± 12	FEV_1/FVC	78 ± 7	74 ± 10	>0.05
							FVC, %	73 ± 19	78 ± 14	
							DL_{CO}, %	70 ± 23	88 ± 20	

Study	No. of Participants	No. with Pleural Plaques Only	Cohort	Location	Asbestos Exposure Measure	Avg. Estimated Exposure	Measure of Lung Function	Result (Mean ± SD)		*p* value
								Control	Pleural Plaques	
Neri *et al.*, 1996	119	50	Asbestos workers	Italy	Duration (years)	No PP: 4.8 ± 4.4 With PP: 9.1 ± 5.5	FEV_1	NR	NR	>0.05
							FVC	NR	NR	
							FEV_1/FVC	NR	NR	
							TLC	NR	NR	
							MEF_{25-75}	NR	NR	
							DLco	NR	NR	
Soulat *et al.*, 1999	170	84	Former insulation workers	France	Duration (years)	12.9 ± 0.6	FEV_1, %	108.4 ± 3.15	112.6 ± 2.40	>0.05
							FVC, %	108.9 ± 2.60	110.2 ± 2.03	
							MEF, %	111.1 ± 3.66	116.1 ± 2.96	
							MMEF, %	76.9 ± 4.53	81.1 ± 4.02	
Copley *et al.*, 2001	50	NR[a]	Patients with benign pleural disease	England	NR	NR	FEV_1	NR	NR	>0.05
							FVC	NR	NR	
							TLC	NR	NR	
							RV	NR	NR	
							Dco	NR	NR	
Oldenburg *et al.*, 2001	43	21	Asbestos workers	Germany	Duration (mean years)	30.7	FEV_1, %	86.58 ± 28.09	91.67 ± 20.25	>0.05
							FVC, %	89.89 ± 11.86	88.8 ± 13.89	
							FEV_1/FVC	94.9 ± 19.48	98.58 ± 13.48	
							MEF, %	93.07 ± 37.69	90.14 ± 36.79	
Van Cleemput *et al.*, 2001	73	51	Cement factory workers	Belgium	CEI	26.3 ± 12.6 f-years/ml	FEV_1, %	103.8 ± 13.7	104.1 ± 12.9	0.24
							VC, %	109.8 ± 14.9	110.5 ± 13.4	0.24
							FEV_1/VC	0.78 ± 0.07	0.78 ± 0.07	1.00
							PEF, %	108.7 ± 21.5	100.5 ± 23.3	0.48
							MEF, %	103.0 ± 35.7	109.2 ± 25.02	0.27
							TL_{CO}, %	97.2 ± 15.5	102.0 ± 16.5	0.93
Rui *et al.*, 2004	103	36	Asbestos workers	Italy	Duration (years)	No PP: 22 ± 6 With PP: 30 ± 6	FEV_1, %	**102 ± 13**	**95 ± 14**	**<0.05**
							VC, %	**96 ± 11**	**90 ± 10**	**<0.05**
							FEV_1/VC	78 ± 6	77 ± 7	>0.05
							TLC, %	**97 ± 9**	**91 ± 9**	**<0.05**
Sette *et al.*, 2004	82	NR	Cement workers	Brazil	Duration (years)	14.5 ± 10.1	Gas exchange	NR	NR	>0.05[a]

Study	No. of Participants	No. with Pleural Plaques Only	Cohort	Location	Asbestos Exposure Measure	Avg. Estimated Exposure	Measure of Lung Function	Result (Mean ± SD)		*p* value
								Control	Pleural Plaques	
Sandrini *et al.*, 2006	91	32	Patients with asbestos-related disorders	Australia	NR	NR	FEV_1, %	92 ± 16.9	93 ± 13.2	>0.05
							FVC, %	94 ± 13.5	95 ± 2.4	>0.05
Chow *et al.*, 2009	86	26	Asbestos workers	Australia	NR	NR	FEV_1, %	91.65 ± 15.41	89.12 ± 16.41	>0.05
							FVC, %	91.88 ± 16.46	91.73 ± 16.04	
							VC, %	98.18 ± 15.80	100.0 ± 10.98	
							DL_{CO}, %	89.43 ± 15.26	86.69 ± 16.06	
Clin *et al.*, 2011	2,743	403	Asbestos workers	France	CEI (exposure units x years)	No PP: 47.9 ± 83.1 With PP: 112.6 ± 128.6	FEV_1, %	**101.9 ± 19.2**	**97.9 ± 19.4**	**0.0032**
							FVC, %	**100.4 ± 16.6**	**96.6 ± 16.6**	**<0.0001**
							FEV_1/FVC	80.0 ± 7.9	79.2 ± 9.0	0.27
							TLC, %	**101.2 ± 16.0**	**98.1 ± 14.2**	**0.0494**
Spyratos *et al.*, 2012	266	29	Cement factory workers	Greece	Mean concentration	1.7-6.49 f/ml	FEV_1, %	99.8 ± 15.2	92.6 ± 14.3	0.461
							FVC, %	99.6 ± 13.8	94.3 ± 12.5	0.536
							FEV_1/FVC	83.1 ± 10.4	78.1 ± 9.3	0.294
							MMEF, %	91.7 ± 30.4	71 ± 23.7	0.703
							TLC, %	93.3 ± 13	90.1 ± 7.7	0.983
							DL_{CO}, %	101.3 ± 15.8	100.5 ± 20.3	0.844

Notes:

Statistically significant results are in **bold** type.

CEI = cumulative exposure index; DL_{CO} = diffusing capacity for carbon monoxide; eCO = exhaled carbon monoxide (a marker of lung oxidative stress); FEF_{50} = flow at 50% of forced vital capacity; FE_{NO} = fractional exhaled nitric oxide (a marker of lung oxidative stress); FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HRCT = high resolution computed tomography; MEF = forced expiratory flow at the level when 50% of the FVC remains exhaled; MEF_{25-75} = forced expiratory flow at the level when 25-75% of the FVC remains exhaled; MVV = maximal voluntary ventilation; NR = not reported; PP = pleural plaques; RV = residual volume; TLC = total lung capacity; TL_{CO} = transfer factor for carbon monoxide; VC = vital capacity.

(a) Presence of pleural plaques was evaluated as an independent variable.

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